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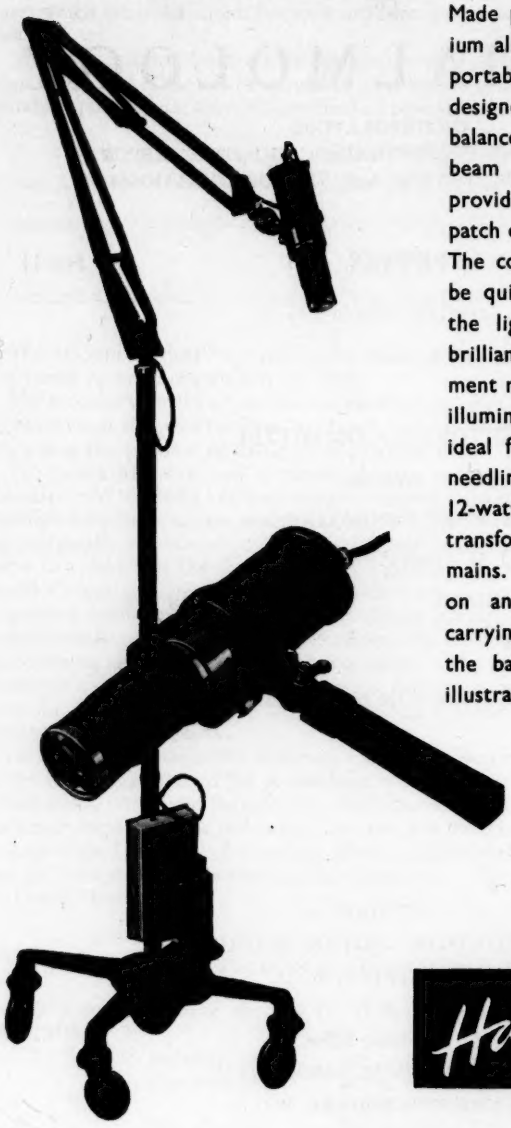

Made principally of aluminium alloy, this hand-lamp is portable and light. It is so designed as to be perfectly balanced in the hand. Its beam is readily focused to provide an intense but even patch of light for operating. The condenser is hinged to be quickly removable from the light path, so that a brilliant image of the filament may be projected; the illumination thus provided is ideal for such purposes as needling. It employs a 12-volt 12-watt lamp, requiring a transformer for use from A.C. mains. It can be supplied on an Anglepoise trolley carrying the transformer on the base as shown in the illustration.

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COMMUNICATIONS

STERILE DROPS AND LOTIONS IN OPHTHALMIC PRACTICE*

BY

FREDERICK RIDLEY

London

THE carriage of pathogenic bacteria to eyes through the agency of drops has presented a serious problem for several decades and this problem has not, hitherto, been effectively solved. Screw-cap bottles and the use of a preservative in all drops were recommended by a committee of the High Holborn Branch of Moorfields in 1954[1]. A Dispensary and Sterilization Committee serving the joint hospital was set up in 1955[2]. The author was in the best position to devise and put into operation the practical requirements of such a scheme, and the High Holborn Branch of the Hospital was used throughout to test various methods of control. The material to be presented has been divided into that of general interest in large type and in smaller type the practical details, chiefly of interest to the pharmacist.

SCOPE OF THE PROBLEM

It was demonstrated that practically all the drops in use in the hospital, including many bottles that had not yet been opened, were infected. Secondly, it was shown that *Ps. pyocyanea* in particular was liable to infect a wide range of drops and ointments, and that the antibiotics, in strengths commonly used in ophthalmology, offered no effective protection. Care in the use of drops—seeing that the eye being treated is not touched by the dropper and that the neck of the bottle is not touched either in removing or inserting the dropper, and so on—is not effective. The drops must be self-sterilizing. As a corollary, if it is necessary to use unprotected drops, then they must be put up sterile in a sterile sealed container and used only once and with full aseptic precautions.

PROTECTION OF DROPS

The introduction of a preservative into drops has been proposed and indeed used for many years. The national formulary follows the British Pharmaceutical Codex in recommending Liquor pro Guttis (0·023 per cent. methyl hydroxy-

* Received for publication March 4, 1958.

1. Messrs. C. H. Greer, H. E. Hobbs, and J. G. Milner.
2. Messrs. N. Ashton (*Chairman*), A. J. B. Goldsmith, A. Lister, E. S. Perkins, F. Ridley, H. Ridley.

benzoate and 0·011 per cent. propyl hydroxybenzoate) for all drops in aqueous solution. Klein, Millwood, and Walther (1954) have drawn attention to the fact that this concentration is at least three times too little to be effective against *Ps. pyocyanea.* Phenylmercuric nitrate in a concentration of 0·004 per cent. is effective against *Ps. pyocyanea*, however, even in fluorescein solution, and is relatively non-poisonous and innocuous in this concentration. It is probable that there are other substances as effective as these. The objective was to devise and put into operation a practicable scheme securing safe drops and lotions throughout the hospital: 0·1 per cent. methyl hydroxybenzoate (M.H.B.) and 0·004 per cent. phenylmercuric nitrate (P.M.N.) had been well tried and had proved effective. The objection to the use of M.H.B. in all drops is that in this concentration (0·1 per cent.) it is more irritating than P.M.N. 0·004 per cent., and that in certain solutions, notably fluorescein and eserine (Klein and others, 1954), it is less efficacious against *Ps. pyocyanea.*

Sensitization.—Using P.M.N. 0·004 per cent. or M.H.B. 0·1 per cent. to cover the whole range of aqueous drops, very few cases of dermatitis medicamentosa attributable to the preservative used were seen in 3 years' practice in the hospital. Those cases which did occur were seen in the Out-Patient Department, where drops protected by P.M.N. have been used for a long period of time, and in every case the reaction was slight and the patient was made comfortable by changing either the drops or the preservative used in the drops.

Choice of Protective Solutions.—P.M.N. and M.H.B. in these concentrations, both as reported by Klein and as tested in Prof. Ashton's laboratory, proved effective against a wide range of bacteria tested, including *Ps. pyocyanea, Streptococcus pyogenes,* and *Staphylococcus aureus* at room temperature, in conjunction with the drugs commonly used and in normal clinical concentrations, in 3 hours.

Solutions of P.M.N. and M.H.B. are made up in distilled water, and the solution is used as a diluent in normal dispensary practice. It is convenient to dissolve the P.M.N. by adding the powder to distilled water to produce a 0.01 per cent solution and autoclaving. This is further diluted as required.

P.M.N. gives a faint cloudy precipitate if added to solutions containing free chloride or bromide ions, since the chloride and bromide, as opposed to the nitrate, are relatively insoluble. It has been argued that this relatively insoluble chloride is useless, but experiments conducted by Prof. Ashton show that this is not so and that such solutions are fully effective. This is analogous to silver nitrate precipitated as chloride: the relatively insoluble chloride will kill pathogenic staphylococci at a dilution of 0·1 per cent. in 10 per cent. serum-saline, and inhibits down to 0·004 per cent. (F. Ridley, 1931).

Antibiotics are said to be unstable when mixed with heavy metal salts in solution, but the mercury atom is part of the "phenylmercuric" radicle in P.M.N. and is probably harmless in this context; Klein and Millwood (1955) have shown that penicillin solution protected with 0·05 per cent. P.M.N. is stable for several weeks.

Cortisone acetate and hydrocortisone are protected with 0·1 per cent. benzyl alcohol as supplied by the makers. This concentration is irritating and unsuitable for use in ophthalmology and the makers' preparation has been diluted to the concentrations used in the hospital (cortisone acetate (0·25 per cent.), hydrocortisone (0·125 per cent)) by the addition of M.H.B. 0·1 per cent.

TABLE

PROTECTION OF DROPS

Methyl Hydroxybenzoate 0·1 *per cent.* (*M.H.B.*)	Adrenalin, Amethocaine, Antazoline Compound, Atropine Methylnitrate, Chloramphenicol, Cocaine Hydrochlor, Cortisone, Ephedrine, Ethylmorphine (Dionine), Gelatin Eye Drops, Homatropine, Homatropine and Cocaine, Hydrocortisone, Hyoscine, Lachesine, Liquocaine, Neomycin Sulph., Penicillin, Potassium Iodide, Sodium Iodide, Streptomycin, Sulphacetamide, Zinc Sulphate, Zinc Sulphate and Adrenalin.
Phenylmercuric Nitrate 0·004 *per cent.* (*P.M.N.*)	Atropine, Copper Sulphate, Duboisine, Eserine, Fluorescein, Glycerine, Methylcellulose, Pilocarpine, Ringer-Saline, Sulphacetamide and Zinc.
Phenylephrine Ophthalmic Solution 10 *per cent.* (Boots) and *Prostigmin* 3 *per cent.* (Roche Products Ltd.)	Used as issued.

Protection of Oils and Ointments

There is no effective preservative which can be used to protect oils and ointments, and the same danger exists for them as for aqueous drops. Indeed, *Ps. pyocyanea* has been isolated from ointment on several occasions. It is proposed to eliminate the use of oily drops entirely in the practice of Moorfields Hospital, oils being replaced by ointments. Ointments are dispensed only in sterile tubes and, in practice, a little is expressed on to a sterile glass rod and by this means applied to the eye. This safeguard is unnecessary where the tube is dispensed for an individual patient.

Containers

Bottles

The orthodox Chalk's bottle has been abandoned entirely, since the unit cannot be sterilized by heat as the massive glass base is liable to crack. As normally constructed, the dropper is ground into the neck of the bottle and is therefore an individual fit, so that the whole unit has to be separately washed and the dropper identified with its own bottle, thus making any semi-automatic washing, drying, and sterilizing impossible. The rubber diaphragm commonly used is wasteful of time in assembly and has a short life. In the commonly available samples Chalk's bottles have no hood attached to the dropper covering the neck of the bottle, and the neck therefore collects dust and is contaminated by the drops themselves however careful one may be. On returning the dropper to Chalk's bottle it is very common for this dirt to be carried by the dropper from the edge of the neck into the drops. Over several months an extensive series of cultures of the contents and of the neck of Chalk's bottles was taken; the results did not compare with the standard obtained with screw-cap bottles.

Screw-cap bottles, preferably square*, which are provided with a plastic collar and a rubber unit carrying the glass dropper and rubber teat, have been found effective and convenient in use. The glass dropper should have a round ball-end, other dropper ends not being so safe or effective in use. Screw-cap bottles have the merit that the drops are sealed so that evaporation is eliminated, the neck of the bottle is fully protected, the parts are interchangeable, and the bottles inexpensive. The whole unit or its parts can be autoclaved or sterilized by dry heat. Since the parts are interchangeable the bottles can be dismantled, washed, autoclaved, and re-assembled very simply. The square bottle is the more convenient in use since it is less easily upset. These bottles in the standard quarter-ounce and half-ounce sizes have covered all requirements.

Method of Preparing Bottles.—Dirty bottles returned to the dispensary are first stripped to their component parts and washed in running water—an under-water jet is a convenient device. The labels are soaked off and may be collected in a suitable label trap built into the sink; it is essential that labels used should soak off in this way. The washed components are inspected as they are passed into perforated trays (Fig. 1), in which they are then placed in a standard sterilizer containing a non-foaming detergent such as Loral. After being boiled the units, still in their trays, are lifted out and drained. They are turned over and immersed in distilled water in a sink and so refilled. In this way traces of detergent, etc. are removed and the bottles, wetted with distilled water, are now placed in the same trays in an oven in which they are dried. This oven may be a domestic gas oven set just above 100°C. The components are re-assembled but the cap is not screwed down. The bottles are packed into half-biscuit tins (Fig. 2),† each holding fifty or sixty bottles. The lid is put on the tin, and the whole tinful of bottles is sterilized in a hot air sterilizer and stored for future use.

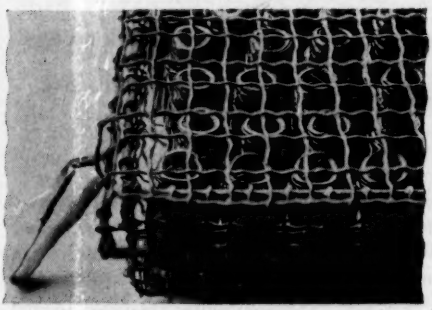

FIG. 1.—Wire tray filled with bottles for sterilizing in boiling water.

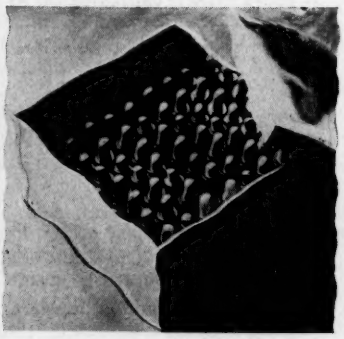

FIG. 2.—Bottles packed into tin for sterilizing in hot air.

Filling the Bottles.—A semi-automatic unit‡ is used (Fig. 3, opposite). Compressed air is passed through a cotton-wool filter into the blood bottle containing the drops that are being dispensed. This compressed air may be derived from a simple hand-bellows or foot-pump, but we have found it more convenient to use a foot-pump compressing air in a two gallon tin provided with a safety valve, which may be the release valve of a

* These screw-cap bottles are supplied by Maw, Son, and Sons, Barnet.
† Available from Huntley, Bourne, and Stevens Ltd., Reading, Berks.
‡ The unit illustrated is available from Messrs. Matburn, 25, Red Lion Street, London, W.C.1.

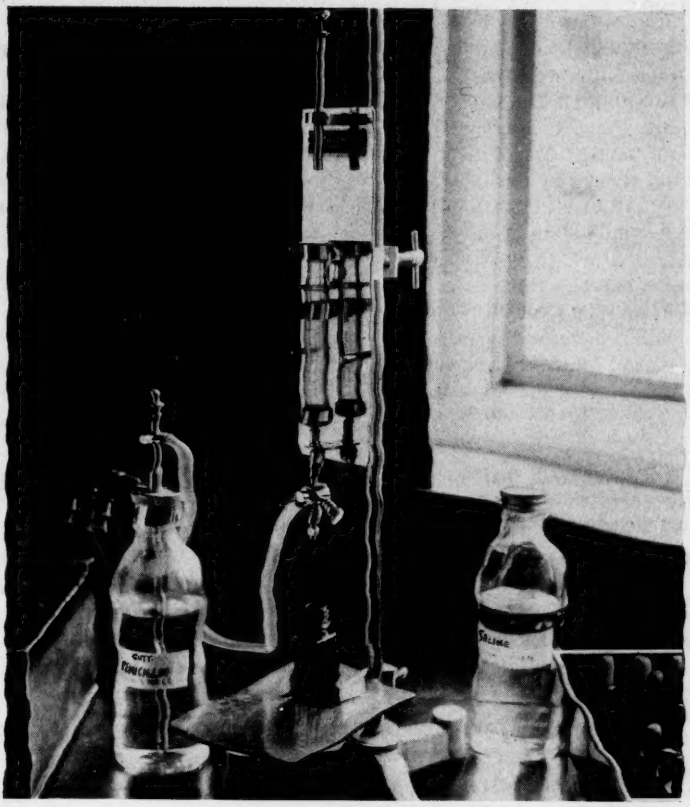

FIG. 3.—Unit assembled for filling bottles.

domestic pressure cooker set for 10 lb. per square inch. Up to an hour's filling of bottles may be undertaken without re-pumping. The filling unit, including the stand, syringe, clamps, etc., but excluding the compressed air reservoir, can be autoclaved without dismantling it. It is desirable to lubricate the plunger of the syringe with silicone grease. Two or three hundred bottles an hour can be filled under sterile conditions and each bottle will receive a fixed quantity of solution. The solutions themselves are easily handled in standard blood bottles as illustrated, and a new bottle can be attached without difficulty. When it is desired to change over from one drug to another, a bottle of protected distilled water is attached and the whole equipment pumped through with several ounces of fluid. A table with localizing pegs holds the bottle in the centred position to receive the jet of fluid. The bottles so filled are screwed down and packed into a tin box which is sealed and labelled, with a corresponding label put inside. The inside of the bottles is thus sterile but the outside is not, and thus the contents are protected. These tins each containing fifty filled bottles are stored ready for individual labelling.

LABELLING

Labels should be of suitable printed paper, backed with gum which may be either tragacanth or dextrin. It is essential that they should soak off in hot water. Where drop-bottles are used repeatedly as in the clinic, theatre, or wards, unprotected labels tend to become stained and unsightly. This can be avoided if the labels are painted over with a suitable varnish* which gives a hard clear glaze and is not stained by fluorescein or other coloured drops. It can be wiped clean with a wet swab. Labels so varnished can be boiled off easily. Writing should be either in indian ink or in heavy black pencil; ordinary ink runs.

Colour of Labels.—The International Federation of Ophthalmological Societies (1954) made the following recommendations:

(*a*) *Red:* Drugs that in certain circumstances can be dangerous, *e.g.* mydriatics.

(*b*) *Orange:* Drugs to be used with caution, *e.g.* miotics, priscol, adrenalin, antibiotics, etc.

(*c*) *Green:* Drugs without danger, *e.g.* colloidal silver preparations, zinc sulphate, mild antiseptics, antistine-privine, etc.

(*d*) *Red with Green Bands:* Anaesthetics.

It was felt, however, that drugs should be identified not only as to their potential danger but also by their essential ophthalmological properties, and with this in view the following modification has been adopted (Fig. 4 (*a*), opposite):

(*a*) *Red: Mydriatics*

Adrenalin, atropine, atropine methylnitrate, duboisine, ethylmorphine, homatropine hydro-bromide, homatropine and cocaine, hyoscine, lachesine.

(*b*) *Blue: Miotics*

Di-isopropylfluorophosphonate, eserine, pilocarpine, prostigmin.

(*c*) *Orange: Antibiotics and Chemotherapeutic Substances*

Chloramphenicol, neomycin sulphate, penicillin, streptomycin, sulphacetamide, sulphacetamide and zinc.

(*d*) *Red with Green Bands: Anaesthetics*

Amethocaine, cocaine, lignocaine.

(*e*) *White: All Other Substances used as Drops*

e.g. antazoline compound, artificial tears, copper sulphate, cortisone, ephedrine, fluorescein, gelatin, glycerine, hydrocortisone, methylcellulose, ravolin, potassium iodide, Ringer-saline, zinc sulphate, zinc sulphate and adrenalin.

Examples of Labels Used

(*a*) *Individual Patients.*—The label illustrated, printed in the appropriate colours on white paper, has been adopted for universal use (Fig. 4 (*b*), opposite). It measures $3'' \times 1''$ and, provided that it is attached at the left hand edge of a clear panel in any of the standard drop bottles ($\frac{1}{4}$-ounce or $\frac{1}{2}$-ounce, square or hexagonal types), two or three clear panels will have unprinted paper over them for writing upon. The printed paper lies over the corrugated panels of glass. For out-patients it is necessary to fill in the appropriate number opposite "both eyes", "right eye", or "left eye", to indicate the number of times daily the drop is to be used (Fig. 5). The patient has a clear instruction, the law is complied with, and one can see at a glance what kind of drug has been dispensed.

* Bostik No. 5293. Suitable thinners to use with this varnish are supplied by the makers, BB Chemical Co., Ltd., Ulverscroft Road, Leicester.

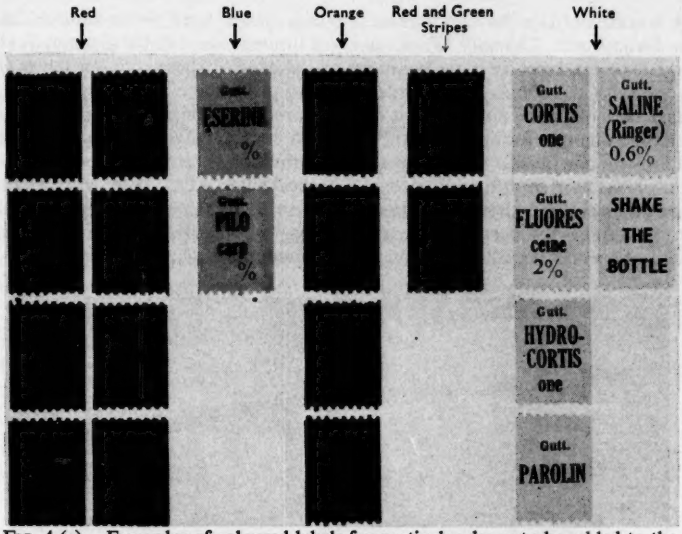

FIG. 4 (*a*).—Examples of coloured labels for particular drops to be added to the universal label for hospital use.

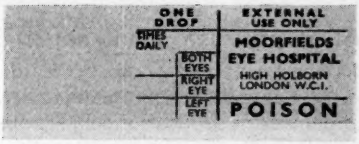

FIG. 4 (*b*).—Universal label to be printed in four colours for distinguishing various types of drops.

For in-patient use it is necessary to add to this the name of the ward, the name of the patient, and the kind of drug. As a rule the ward can be codified (*e.g.* Floor 1, 2, 3 or Ward A, B, C) and the name of the drug can be abbreviated. An entire panel remains for the patient's name if coding is used for the ward and the drug. Typical labels for in-patient use are illustrated in Fig. 5.

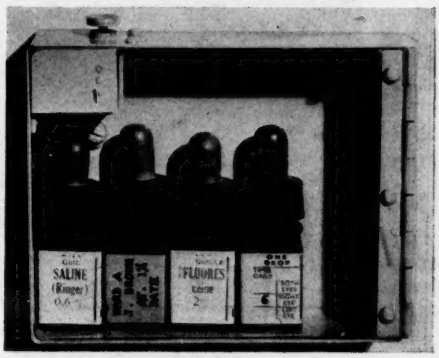

FIG. 5.—Labelled bottles stored in special locked cupboard for ward use.

(*b*) *Wards and Out-Patients Clinics.*—Where drops have to be used in the Out-Patients Department, Casualty Ward, and to a limited extent in the General Wards, it is necessary to use a label carrying the name of the drug. These stick-on labels (Fig. 4*a*) correspond with the colour scheme adopted, and present the name of the drug and its percentage clearly on one panel so that one is not required to read round the bottle which can be dangerous (for instance, amethocaine and cocaine have been confused when not printed fully on one panel). Other essential information is printed on the universal label. For convenience in printing, occasional liberties have been taken with spelling and customary abbreviations have been used. The labels may be printed in perforated rolls of 500. A device for carrying twenty or more such rolls, presenting them to the operator and keeping the labels dry and clean, is used in the dispensary (Fig. 6)*.

FIG. 6.—Container for dispensing rolls of coloured labels.

SPECIAL ARRANGEMENTS FOR HANDLING DROPS

In the Out-Patients Department and Casualty Ward an unnecessarily wide range of drops, both as to kind and strength, tends to accumulate. By common consent of the staff, the number of drops routinely set out at each desk has been reduced to a minimum.

Out-Patients Department.—Five kinds of drops (Fluorescein 2 per cent., Ringer-Saline 0·6 per cent., Eserine 0·25 per cent., Homatropine and Cocaine a.a. 2 per cent., and Cocaine 2 per cent.) are set out in perspex racks (Fig. 7).

FIG. 7.—Perspex rack for carrying labelled bottles for use in the Out-patients Department.

* M. Harland & Son Ltd., 12, Norfolk Street, W.C.2.

In addition, the surgeon nominates whatever drops he wishes to have available for his unit, and these are put out separately on his desk. Any drop may be obtained on request from the dispensary. Alongside the perspex rack of bottles is placed a quantity of glass rods and glass pipettes with rubber teats which have been dry sterilized.

Casualty Ward.—A restricted list of drops is normally set out, and this list is modified from time to time. Homatropine 1 per cent., Atropine 0·5 per cent., Pilocarpine 2 per cent., and Eserine 0·5 per cent. are also available for issue to out-patients at any time. For staining the cornea, a sterile glass rod dipped in Fluorescein 2 per cent. is used, and saline is delivered with sterile pipette. It is unsafe to use the dropper from the drop bottle in infected cases, since experiment has shown that the dropper almost invariably becomes contaminated and the preservative is not effective within some 3 hours.

The Wards.—Cross-infection brought about by the use of the same drop-bottle from case to case in the wards has been established often enough for it to be certain that individual drops must be provided for in-patients.

Medico-legal Aspects of the Problem.—It is the current ruling of the Home Office and of the Ministry of Health that Schedule 1 poisons for adult patients need not be kept under lock and key in the ward if they are dispensed for an individual patient. If a small cupboard for each patient's drops is provided it need only have a simple catch, but if it is thought desirable a lock may be fitted.

Drop Bottles for Individual In-Patients.—The drops cupboard illustrated (Fig. 5)* was designed for this purpose. The body is of brass sheet. The lock is operated by two separate actions ((*a*) the Perspex door is pressed back, (*b*) the button, top left, is depressed) and the door flies open. The cabinet locks automatically when the door is closed. No part of the cupboard or lock can rust. The labels can be read through the Perspex door. The bottles are protected from dust, and the cupboard is easily cleaned and attractive in appearance. The whole unit can be taken down and washed with a detergent, or if necessary sterilized in P.M.N. 0·01 per cent. Dettol or carbolic preparations destroy perspex and should never be used.

Operating Theatre

Drops at Operation.—Formerly several sterile Chalk's bottles containing unprotected drops were kept in a sterile container provided with a lid. Bacteriological investigation showed that both the drops and the outsides of the bottles became infected very quickly. This method was replaced by the following theatre procedure:

Standard screw-cap bottles, from which the dropper has been removed, containing protected drops are available. Several dry heat-sterilized droppers are put out on the surgeon's trolley and when drops are required a non-sterile nurse unscrews the cap and holds the bottle conveniently for the operator who withdraws the drops required with a

* George Wailes and Co., Ltd., 382, Euston Road, London, N.W.1.

sterile pipette and places the pipette on one side after use. In this way it is almost impossible to contaminate the drops within the bottle. This method has proved entirely satisfactory.

Pre-Operative Drops.—The ward sister is provided with the drops used for the preparation of cases for operation and the appropriate drops are issued to the nurse preparing each case. After use the drop-bottles are returned to the dispensary. Thus only fresh, protected, sterile drops are used in preparing an eye for operation. If further drops are needed after a patient reaches the operating theatre, the theatre technique already described is employed.

Post-Operative Drops.—These are issued individually and placed in the bedside drops cupboard (Fig. 5).

Replacement of Drops

Repeated bacteriological testing of drops that have been in use in the Out-Patients Department and Casualty Ward has shown that they are still sterile and self-sterilizing after 3 months' use. This is perhaps as long as it is desirable to have such drops "in use", since there is a risk of evaporation with consequent concentration when the bottle is open. If bottles are kept closed, the contents would presumably be self-protecting indefinitely. As a routine, however, all drops are replaced at the end of one month.

Special Problems

In the course of this work the following problems arose and their solution may be of interest:

Distilled Water

Steam-heated stills should always have a pressure-control valve between them and the boiler to secure a uniform head of steam in working, and, with this steam-pressure operating, should be carefully adjusted. If these precautions are not observed such stills can be very wasteful and can deliver unsatisfactory distilled water. A further point is that they should be stripped, cleaned out, and examined from time to time, as they may rust through or become furred up, and are liable to develop cracks giving direct contamination between the cooling water and distilled water. The distilled water must be collected in a suitable container and this must be sterilized from time to time, preferably daily. The danger here is that, in cooling down, distilled water is very liable to contamination by *Ps. pyocyanea*, and once this infection is established a cumulative infection will occur unless the vessel is frequently sterilized.

If pyrogen-free water is required then a glass-lined still is necessary.

Condensate Water

Steam-condensate water is usually available in large quantities in the boiler house and, apart from pharmaceutical purposes, this is a satisfactory alternative to distilled water, *e.g.* for use in sterilizers, for washing out bottles, and so on. The problem of storing and conveying such water was solved by the use of 5-gallo

milk churns, but if this is done it is necessary to have the churns tin-dipped, not galvanized, since galvanizing corrodes when autoclaved, and also to have the tin-dipped churn plated with tin internally to seal off the pores always present after "dipping"*.

Saline

An abundant supply of sterile saline at body temperature is very desirable throughout an eye hospital. The possibility of using standard aquarium thermostats for this purpose was first suggested at St. Thomas's Hospital and has been developed in the following way at Moorfields:

A standard fish tank is mounted on a standard angle-iron carrying-frame with one lower frame on which rests a plate-glass shelf. The manufacturers will supply this tank with an aluminium hinged lid as illustrated (Fig. 8 and Fig. 9, overleaf).† The lid should have a drip sill, otherwise condensed water will run outside the tank when the lid is raised. Heating is by two standard heaters placed on the floor of the aquarium underneath the Perspex shelf. This is carried on several Perspex pillars and is a safeguard against a dropped bottle going through the bottom of the tank while distributing the heated water. The

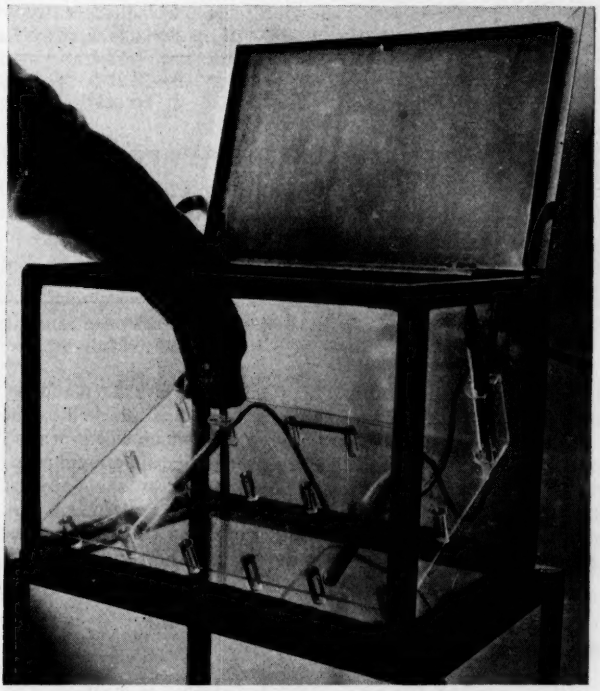

FIG. 8.—Saline tank with hinged lid for supplying saline at body temperature.

* Dairy Supply Co. Ltd., Cumberland Avenue, N.W.10.
† Supplier: Fishtanks Ltd., George Street, London, W.1.

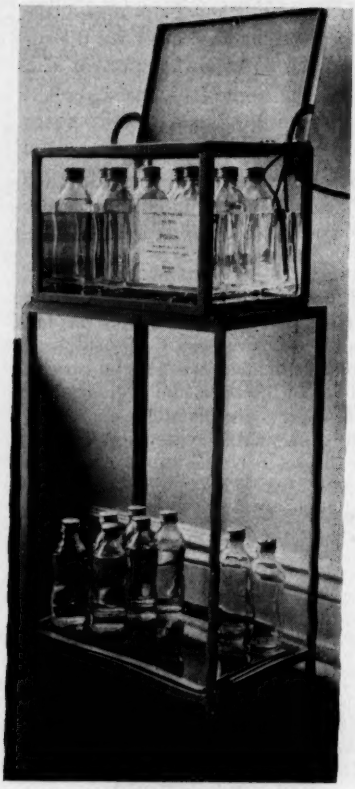

FIG. 9.—Saline tank in use with lower shelf for full or used bottles.

thermostat is a standard aquarium thermostat set for just over blood heat, preferably 102°F., protected by a Perspex shield, and in circuit with the heaters. The earth terminal is connected rigidly to the metal frame of the tank and to a stout copper strip running down inside the tank, which is bent to lie on the bottom (P.M.N. attacks solder). The tank itself contains 0·01 per cent. P.M.N. solution in distilled water. The level to which the tank should be filled is marked so that when there are eleven bottles in the tank it is comfortably full. The level is made up with distilled water to this mark daily. The saline is put up in standard blood-bottles. Blood-bottles were adopted because they are of convenient size and are constructed with a waist so that they afford an easy non-slip grip to a small hand. Full and empty bottles are kept on the tray underneath, there being eleven full bottles in the tank at any one time. By starting the tank with the rear left-hand space unoccupied and replacing a cold full bottle to the left of the space from which a

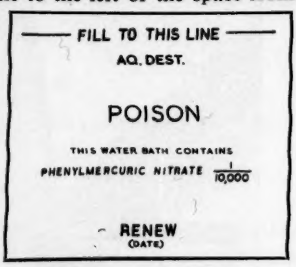

FIG. 10.—Label for saline tank showing renewal date.

warm full bottle has been taken, a fully-heated bottle is always taken and the tank always full. The caps for these bottles are of aluminium which is attacked by the mercury in the P.M.N. if a bottle is immersed. Plastic screw-caps which will withstand autoclaving are not, as yet, available in the required size. In practice aluminium caps have proved satisfactory, and are rarely wetted by the tank solution if reasonable care is taken. This P.M.N. solution is replaced once a month; the date when replacement is due is written on a label attached to the tank (Fig. 10). Bottles of saline are taken out, dried off with a towel, and used for all normal purposes in the ward. They do not contain any preservative.

Preparation of Saline

For ophthalmic use 0·9 per cent. sodium chloride is stinging and contains a large excess of sodium and chlorine ions. It has been abandoned in favour of a Ringer solution equivalent to 0·6 per cent NaCl which is both physiological as regards ion distribution and comfortable to the patient.

To prepare this, one tablet (B.D.H. 74A) is put into a washed blood-bottle, which is filled up to the mark with distilled water (540 ml.), and the cap screwed on. Such bottles are put into a standard pint-bottle milk crate, and as many crates as may be necessary are prepared in this way and stacked one on top of the other. These are transposed to the major autoclave last thing in the day's work; they are brought up to 115°C. when the pressure is turned off and the apparatus left to cool overnight. This is important if a certain amount of breakage and, where the caps are not tightly screwed down, boiling-over are to be avoided. Using this procedure it is rare to encounter any trouble. The next morning the bottles are removed and carried in their crates to the various wards of the hospital.

Anterior Chamber Washouts

The provision of sterile physiological Ringer saline solution equivalent to 0·9 per cent. NaCl for anterior chamber washouts and for use in the theatre presented a considerable problem. Plastic screw-caps which will withstand autoclaving are available for 6-oz. bottles, and this size is convenient.

A solution is made by dissolving one tablet (B.D.H. 75B) in 540 ml. pyrogen-free distilled water, and the small bottles are filled. The cap is screwed down on to its rubber washer and the whole autoclaved as for saline for the wards. These bottles are totally immersed in 0·01 per cent. P.M.N. solution in a saline tank (Figs 8 and 9) in or near to the operating theatre. The tank as designed is flash-proof. The bottles can be removed from the tank at blood heat, and being sterile can be placed directly on to the operating trolley and dried off with a sterile towel. Any saline left at the end of the operation is discarded.

Drops and Solutions for use in Conjunction with Contact Lenses

Neither of the preservatives can be used in effective concentration under a contact lens, where they are intolerably uncomfortable. For use under the contact lens, sterile unprotected fluorescein 0·2 per cent. in 2 per cent. sodii. bicarb. and sodii. bicarb. 2 per cent. are required.

Pint bottles of these solutions are pasteurized: pathogenic bacteria are thus destroyed and the sodii. bicarb. is not broken down as it is by boiling. These lotions are transferred to sterile chloroform dropper-bottles, and are used for filling the individual contact lenses.

Liquid paraffin in quarter-ounce drop bottles is similarly pasteurized daily.

Contact Lens Solution

Sodii. bicarb. 2 per cent. has proved effective for this purpose. Contamination may be prevented by the inclusion of 0·2 per cent chlorbutol. Suitable tablets for this purpose are prepared by British Drug Houses (S. 74). This concentration of chlorbutol is adequate for the patient's use at home where there is no question of cross-infection. If the concentration of chlorbutol is increased it tends to separate out of solution in cold weather, producing needle-sharp crystals which are intolerable under a contact lens.

Bacteriological Control

From its inception the scheme has been under continuous bacteriological control. The senior surgeon has selected four or more bottles of drops or lotion in use anywhere in the hospital each month, and these have been tested at the Institute

of Ophthalmology. Hitherto these tests, more than two hundred in all, have proved sterile. The measures adopted secure a high degree of protection under routine clinical conditions.

Summary

The methods employed at Moorfields during the years 1955–1957 to secure sterile drops and eye lotions throughout the hospital are set out in detail, and the following essential points are noted:

(*a*) The use of screw-cap drop-bottles, securing freedom from evaporation and protection of the lip of the bottle.

(*b*) The use of an effective protective substance in all drops.

(*c*) The devising of a system of bottle sterilization, filling, and labelling, which has enabled the scheme to be put into operation without greatly increasing the staff in the dispensary (some 10 per cent. in salaries).

(*d*) The use of a system of labels to identify by colour the essential characteristics of drops dispensed and to present the necessary information simply so that only one label need be applied to any bottle whatever its destination may be.

(*e*) The establishment of special arrangements in the Out-Patients Department and Casualty Ward, and the use in the wards of specially designed drop-bottle cabinets for individual drops.

The use of a common bottle of drops for the treatment of successive patients in a ward is strongly deprecated. A simple technique securing the sterility of drops used in the operating theatre has been worked out, as has a method for the pre-operative preparation of patients.

(*f*) The provision of sterile Ringer-saline lotion (equivalent to 0·6 per cent NaCl) at blood heat throughout the hospital. A method of preparing and presenting sterile Ringer-saline solution (equivalent 0·9 per cent. NaCl) at blood heat for anterior chamber washouts and theatre use is described.

(g) The provision of adequate protection for lotions used in the special conditions of the Contact Lens Department.

Routine tests for sterility have shown that the measures adopted secure a high degree of protection under clinical conditions.

A scheme of this magnitude involving big changes in method in many departments of the hospital could not have been carried through without the keen support and continued criticism and advice of the Dispensary and Sterilization Committee under the Chairmanship of Prof. Norman Ashton, to whom whatever success may have been achieved must be attributed. Thanks are due also to Dr. Peter Hansell, Medical Illustration Department, Institute of Ophthalmology, for kindly preparing the illustrations. It is a pleasure to acknowledge the helpfulness of the senior members of the commercial firms named in this paper, all of whom have given much time and thought to the adaptation of their particular products to this purpose.

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CONGENITAL ARTERIO-VENOUS ANEURYSM OF THE RETINA*

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THE first case of arterio-venous aneurysm of the retina to be described was that of Magnus (1874), and since that time not more than forty cases have been reported in the literature. They form an intensely interesting series of cases, and it is the purpose of this paper to discuss their signs and symptoms and to present one additional case with fundus drawing and angiographic evidence of an accompanying intracerebral angioma.

FUNDUS PICTURE

The fundus picture differs according to the number of vessels involved. The disc may be wholly obscured by a mass of tortuous and twisting blood vessels, which represent several arteries and veins that have emerged from the disc and become inextricably wound around each other (Biro, 1951). Here, arteries and veins are difficult to distinguish from each other either by colour or size, and no vessel can be followed for more than a very short distance, as it soon disappears into a mass of convolutions. The macula may be completely covered by vessels, but further out the size and complexity of the vessels decrease although they still remain more tortuous than normal.

In other cases, only one or two vessels are affected, the remaining vessels being normal, and it is in these cases that the vessels can be more intimately studied. Often the three varieties of arterio-venous aneurysm are represented in one fundus. The most striking and common presentation is that in which the large convoluted artery and vein join each other at the end of their course without any intervening capillary bed. The artery is generally the same size as the vein, although both are grossly increased in diameter (from two to ten times). The colour of the blood may be the same as in normal vessels, the actual point of transition between arterial and venous blood being well seen. The transition point is not abrupt but extends over one or two disc lengths of vessel. In this transition area the blood colour is that of a mixture of arterial and venous blood.

In other vessels the blood colour represents a mixture of arterial and venous blood, and they can be classified neither as arteries nor as veins. The vessel walls are often increased in thickness as is shown by sheathing. This is intermittent and quite pronounced in places, and is sometimes seen on

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only one side of the vessel wall. In the case described below only one vein was sheathed.

The second type of arterio-venous aneurysm is the angioma. This consists of an oval mass of small vessels supplied by an artery and usually drained by several small veins, the whole being often less than the disc in size. An angioma is seen in Seidel's case just below the disc. The angioma is not to be confused with the haemangioblastoma of the von Hippel-Lindau syndrome, which is a mass of actively proliferating angioblastic tissue.

The third type is that in which an artery and vein are joined by an anomalous vessel. This is well seen in the present case, where the right superior nasal vein and a right inferior nasal artery are joined by a vertically running vessel. Here the artery and vein were of normal appearance, and after being joined by the anomalous vessel, they continued their course uneventfully to the periphery of the retina. Again the interface between the arterial and venous blood columns in the middle of the anomalous vessel can be seen.

The cause of the condition is probably congenital. The earliest age at which it has been seen is 8 years (Schleich; reported by Rundles and Falls, 1951), and three have been described at 9 years, including the author's case.

The absence of capillaries is a persistence of that type of vascular system found in the eye of a 4-mth (110-mm.) human embryo (Michaelson, 1948). Here the vascular system is represented by an undifferentiated primordium in which the four primary vessel complexes (upper and lower temporal, and upper and lower nasal) can be recognized. The capillaries are budded from the nipple-like protuberances of that part of the vein wall which lies remote from the artery, thus leaving the characteristic peri-arterial capillary-free area. The disturbance which brings about the anomalous middle cerebral vessels takes place at a much earlier stage of embryonic development and involves the anterior and middle vascular plexuses. These two plexuses overlie the mid-brain during their differentiation, and are cut off from the hyaloid system of vessels by closure of the optic stalk at the 12-mm. (5-week) stage. Wyburn-Mason (1943) has suggested that it is just at this time that a common disturbance could affect both the retinal and middle cerebral circulations, and bring about a tract of anomalous vascular tissue stretching from the retina to the mid-brain. However there is no retinal circulation at this time, and between the 12-mm. and 110-mm. stages the hyaloid system of vessels develops and subsequently regresses. The retinal vessels only develop at the 100-mm. stage as budding from the hyaloid artery at the disc; so that if there were a common disturbance, one would expect persistence or malformation of the hyaloid vessels. This has not been seen in association with a retinal arterio-venous aneurysm.

Associated Features

Visual Fields.—These are generally normal. When they are abnormal, the defect is an homonymous hemianopia, and in these cases an intracerebral

angioma is also invariably present. The field loss is due to the interruption of the optic tract connexions by an angiomatous mass of vessels. This is well seen in Case 7 of Wyburn-Mason (1943), with a left retinal arterio-venous aneurysm. There was a right homonymous hemianopia, which at autopsy was found to be due to the penetration of the left optic tract by anomalous vessels.

Situation of Intracerebral Angioma.—The location of the angioma has been determined by Mackenzie (1953) in a series of fifty cases. The majority of the angiomata were located on either side of the Sylvian fissure, corresponding to their origin from the middle cerebral vessels, although there were others in the base of the brain and the frontal, temporal, parietal, and occipital lobes.

Size.—Half of the angiomata were described as large. The author's measured approximately 7×4 cm.

Hemiplegia.—A hemiplegia caused by a subarachnoid or intracerebral haemorrhage develops in a majority of those cases complicated by an intracerebral angioma. The hemiplegia may be sudden in onset, or more often its onset is gradual over a period of a few years. It may be due to small leaks, or to anaemia of the cerebral cortex supplied by the middle cerebral artery caused by the rapid shunting of blood from the arterial to the venous side. In any case the ultimate prognosis after a haemorrhage from an angioma is better than that after the more common berry aneurysm.

Other accompanying signs and symptoms include bruit, headache, epilepsy, speech defect, facial and oculomotor nerve paralysis including ptosis, conjugate paralysis, squint, hydrocephalus, angiomata of the skin and proptosis.

Pupillary Changes.—Unfortunately the reactions of the pupils are not mentioned in thirty of the 31 cases collected from the literature by Rundles and Falls (1951). In the case described by Biro (1951), the fields were normal with visual acuity in the affected eye 5/10, and the pupillary reflexes were normal. In the author's case neither pupil reacted directly, consensually, or to accommodation, but the patient's right eye was blind and the left eye showed a temporal hemianopia although the visual acuity was 6/6 partly. In most of the cases quoted by Wyburn-Mason (1943) there were pupillary abnormalities of size and reaction, and mid-brain angiomata were found in any such cases coming to autopsy.

Visual Acuity.—In 30 per cent. of cases the visual acuity is 6/9 or better, and in the remainder it varies from 6/12 to no perception of light.

To what is this decreased visual acuity due? In some cases at least it does not appear to be due to encroachment on the optic nerve fibres by the angiomatous vessels, as sometimes, where a large mass of vessels completely obscures the disc, the vision is normal, and in others in which the fundus shows only a few vessels affected there is no perception of light.

It may be that, just as there is a failure in the differentiation of the primordial vascular system, there is also a failure in the development of the retinal elements. The rods and cones and their nuclei, the bipolar cells, and the ganglion cells all differentiate between the third and seventh months, and a defect involving any of these cells could be responsible for the decreased visual acuity.

However, in one of two histological examinations of a retina with arterio-venous aneurysm that have been carried out (Brock's Case 3, quoted by Wyburn-Mason), the dilated and tortuous retinal vessels were found to occupy the greater part of the thickness of the retina. The remaining small amount of retinal tissue was degenerate and cystic. Similarly the optic nerve was found to be occupied mainly by a tangle of blood vessels, very little if any conducting tissue being left. The other case (Krug and Samuels, quoted by Reese, 1951) showed essentially the same histological picture. In the author's case also, the right optic foramen was shown to be twice as big as the normal left optic foramen. This would indicate that, at least in this case, the absence of perception of light is due to the exclusion of the optic nerve fibres by the anomalous vessels.

The decrease in the nervous tissue of the retina caused by the angiomatous vessels would explain the poor visual acuity in cases in which arterio-venous aneurysms of the retina are numerous. It is, however, an unsatisfactory explanation in cases with only an occasional arterio-venous aneurysm and absence of perception of light, and it is in these cases that agenesis of the primordial retinal cells may play a part. Histological examination of such a retina will one day provide the answer.

Differential Diagnosis.—The only other condition in which an arterio-venous aneurysm appears is the von Hippel-Lindau syndrome. Here the retina is seen to contain (usually in the periphery) a haemangioblastoma which slowly grows and eventually destroys the eye. As the haemangioblastoma grows, the artery and vein feeding it become very tortuous and greatly increased in size. Exudates appear, the retina becomes grossly oedematous and detached, and secondary glaucoma supervenes. A hereditary nature is seen in about 20 per cent. of the cases, while a similar percentage is complicated by cerebellar, medullar, and spinal cord cysts. Arterio-venous aneurysm of the retina, on the other hand, is a stationary condition, no difference in the fundus appearance being seen after many years of observation. There is no hereditary incidence, and the complicating brain angiomata have almost all been supratentorial, mainly cerebral.

Case Report

The following case of retinal arterio-venous aneurysm illustrates many of the above points.

A single woman, born in September, 1933, came from a family of six children. There are three girls older and two boys younger than the patient, and all are well with no eye

symptoms. The mother died of carcinoma of the right breast when the patient was 13 years of age. The father is alive but is a chronic alcoholic. The father and mother each came from a family of seven, none of whom suffers from any ocular abnormality. Two elder sisters are married, with one child each, and these children are normal.

The patient received a normal state school education until the age of 13 years, when she passed the qualifying examination to the secondary school quite creditably, obtaining 89 per cent. for Arithmetic and 67 per cent. for English. Thereafter she drifted to domestic work in cafés until the gradual onset of a left hemiplegia incapacitated her 3 years later.

The blindness in the right eye was discovered when she was 9 years of age, at a routine medical examination by the School Health Service, but its cause was not investigated. She first menstruated at the age of 16 years, while her three sisters began to menstruate at the age of 14 years, and since then she has menstruated only once every two years. She had frequent diarrhoea until one year ago, but has normal bowel action now. She has suffered all her life from nocturnal enuresis.

FIG. 1.—Left hemiplegia.

When she was 16 the left foot turned to the equinovarus position and she has since had to wear a leg iron with a toe-spring. A few months later her left arm and hand became weak, and she now holds them in the *main d'accoucheur* position.

Her headache began at the age of 17 years and is still present in a severe form. It is constantly present, worse in the right side of the head; it is described as "like a boil throbbing away all the time", and sounds "like a buzzing or surging noise". Because of the headache and the partial hemiplegia she was admitted to hospital, where she was diagnosed as suffering from hysteria.

A year later (at the age of 18), the left side of the face became suddenly weak, and she had difficulty swallowing coarse food such as apples or lettuce. Her voice became thick and her speech slow. An operation was done to correct a right convergent squint, but two weeks later the eye deviated outwards, where it has remained since. One year later she was given a course of radium therapy to the head, which had no demonstrable effect except to produce a partial alopecia.

By the time she was 21 the left hemiplegia and headache had become progressively worse, and she was admitted to hospital again for investigation. This time her true condition was recognized with the help of ventriculography and a left carotid arteriogram.

At no time did she suffer from migraine or epileptiform attacks, and the Wassermann, Kahn, and Kline reactions were negative.

Clinical Examination in July, 1957, at age 23 years.—She presented as a young woman looking older than her age, with a dull facial expression (Fig. 1). The speech was thick and slow, but the patient was quite intelligent and showed good insight. The left hand was held as a *main d'accoucheur*, and only gross clumsy movements were possible. The left leg was in the equinovarus position. A loud bruit was heard all over the head, but best in the right temporo-parietal region.

The lungs, heart (blood pressure 120/80 mm. Hg), abdomen, and secondary sex characteristics were normal.

The power in the left upper and lower limbs was less than in the right, but not greatly so. Tone, joint sense, and co-ordination were normal. There was no Rombergism, and no sensory loss to pinprick or touch. The jerks were all present and equal, except for the left knee and ankle jerks, which were a little brisker than the right. The right

plantar reflex was flexor, and the left was variable. There was a left upper motor neuron facial paresis with weakness of the left masticatory muscles. She could not whistle or swallow coarse food easily. The corneal reflexes were present and equal. Nerves II, VIII, IX, X, XI, and XII were normal.

Eye Examination.—There was a partial right ptosis, and the right eye was divergent 45° (Fig. 2). All the movements of the eyes were poor except abduction of the left eye.

FIG. 2.—Right ptosis, left facial paralysis.

The pupils were equal, central, circular, and about 3 mm. in diameter. They did not react to light directly or consensually or to accommodation. They dilated evenly with gutt. Neosynephrine 10 per cent. and gutt. homatropine and cocaine 2 per cent. of each. It was impossible, unfortunately, to test for Wernicke's hemianopic pupillary reaction.

The visual acuity in the right eye was no perception of light, and in the left 6/6 partly, J2. The retinoscopic findings were normal, and the left vision could not be improved with glasses. The left central and peripheral fields showed a temporal hemianopia (Fig. 3). There was no papilloedema and no pulsation of the vessels in either fundus.

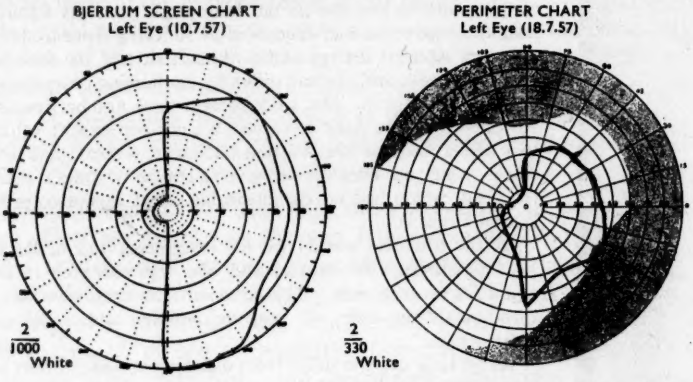

FIG. 3.—Left temporal hemianopia in a woman aged 23 years with visual acuity 6/6 ptly.

The left media, disc, and vessels were normal. The right media and macula were normal, but the vessels emerging from the right disc showed an interesting abnormality (Fig. 4, opposite). At 12 o'clock on the disc, and directed upwards, emerge a large artery and vein, each about three times wider than normal. They each receive a tributary just above the disc, and after numerous convolutions join each other at the retinal periphery, their junction being indicated by a change in the colour of the contained blood.

At 6 o'clock on the right disc, a similar large artery and vein emerge, the vein dividing soon into two, the artery dividing a little further on. Both corresponding branches subsequently join each other at the periphery of the fundus, where again the colour change can be seen.

Immediately below the disc, and attached to an artery, is a very small angioma with one afferent vein. Next to the artery is another, the normal arterial colour of which changes to that of mixed arterial-venous blood half way down.

Nasal to the disc can be seen an anomalous vessel joining the left superior nasal vein and a left superior nasal artery, and again there is a colour change midway along this vessel.

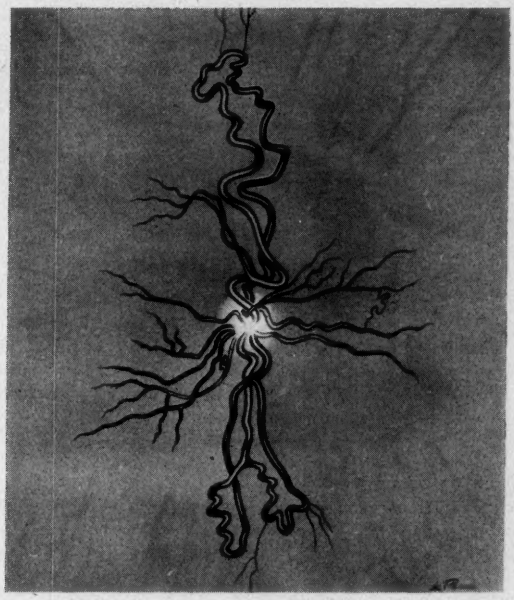

FIG. 4.—Right fundus.

The abrupt change in colour between the arterial and venous blood columns is an interesting phenomenon which does not appear to have been commented on before, although it has most certainly been observed (Cashell, 1948). Clark (1938), observing the arterio-venous anastomoses normally present in a rabbit's ear by the transparent chamber technique, remarked that there was no change in the colour of the brick-red arterial blood in the anastomosis. However, he did not comment on its colour change when it reached the venule which was filled with venous blood derived from the distal capillary net. In the accompanying case there was practically no capillary net distal to the anastomosis. In fact, the only tributaries of the superior anomalous vessels were a small normal-looking artery and vein which came off just above the disc, and a few long and extremely thin vessels which came off near the junction of the artery and vein and disappeared into the ora.

The anatomical configuration does not therefore resemble those normal arterio-venous anastomoses in man which have been found in the penis, tips of the fingers, and bases of the nails. It resembles rather the condition obtaining in traumatic arterio-venous aneurysm (Callander, 1920). In traumatic arterio-venous aneurysm the proximal artery is often dilated and extremely tortuous, while the distal vein is distended and its media hypertrophied.

In the author's case the superior artery and vein are equal in size and about three times the diameter of a normal vein at the disc. The hypertrophy of the muscular coat of the vein is indicated by its sheathing, which is most prominent in the upper half of the vein, where the effect of the arterial pressure is greatest.

In traumatic arterio-venous aneurysm, the entering arterial blood dilates the vein by blocking the venous return as well as by subjecting it to increased pressure. In retinal

arterio-venous aneurysm, only the latter effect operates, as the anastomoses are mainly end anastomoses. In this connexion it is interesting to observe Ney's measurements (quoted by Callander, 1920) of the arterial and venous pressures in experimental aneurysms in dogs. Ney found that the normal arterial and venous pressures were approximately 112 and 10 mm. Hg respectively. After the fistulization the pressures in the proximal and distal portions of both artery and vein were the same, varying between 70 and 105 mm. Hg. This supports the contention that the arterial and venous pressures are equal on either side of the junction of the blood columns, and helps to explain the precise nature of the interface. The arterial blood column cannot push back the venous column, and equilibrium is established at a pressure which is a little less than the normal arterial pressure but much greater than the normal venous pressure, the latter fact accounting for the venous dilation.

The arterial dilation is not so easy to explain, and many theories have been advanced to account for it. It may be that the dilation is due to a loss of tone, as is exemplified by the lower arterial pressure. The distal arterial tree is no longer fed by the artery, and consequently on being short circuited its pressure falls, and with the fall in pressure there is a reduction in tone.

Radiological Examination

Flat X-Ray Film.—Preliminary *x*-ray films of the skull show a small pituitary fossa with bridged clinoid processes (Fig. 5). There is no calcification to be seen. Surprisingly enough, the vascular shadows in the vertex of the skull appear normal, but there is an extremely large right sigmoid and transverse sinus and a large jugular foramen. No basal view was taken. No other abnormality is to be seen in the skull, and the pineal gland is not calcified. This fact did not permit any assessment of the shift in the plain films.

FIG. 5.—Flat *x*-ray of skull.

X-Ray Appearance of the Optic Foramina.—The left optic foramen is normal in size. The right optic foramen is enlarged, being about twice the size of the left (Fig. 6).

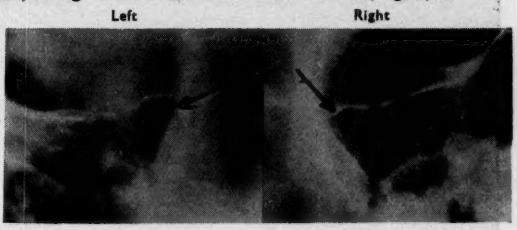

FIG. 6.—Optic foramina.

Left Carotid Arteriogram

ARTERIAL PHASE.—The lateral view shows a large vascular tumour at the base of the brain apparently arising from the middle cerebral vessel (Fig. 7).

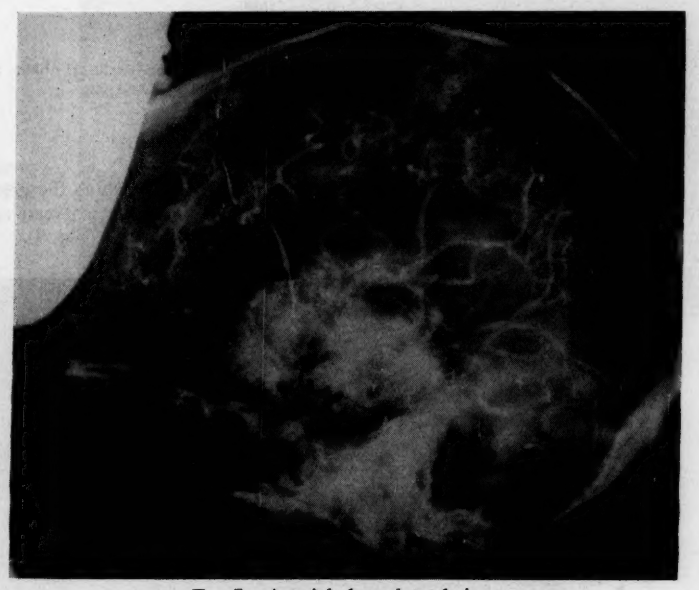

FIG. 7.—Arterial phase, lateral view.

It is roughly semicircular in shape in the lateral view, measuring 7 × 4 cm. The antero-posterior view shows that two-thirds of the tumour lie to the right of the midline, the remaining one-third lying to the left (Fig. 8, overleaf).

In the antero-posterior view the left anterior cerebral artery is well displaced laterally. The right anterior cerebral artery fills and is normal in position. The left middle cerebral artery is displaced laterally, and it would appear that the angiomatous mass arises from the right middle cerebral artery.

CAPILLARY PHASE.—This shows intense opacification of the tumour with sizeable vessels and, very early in the piece, commencing venous drainage.

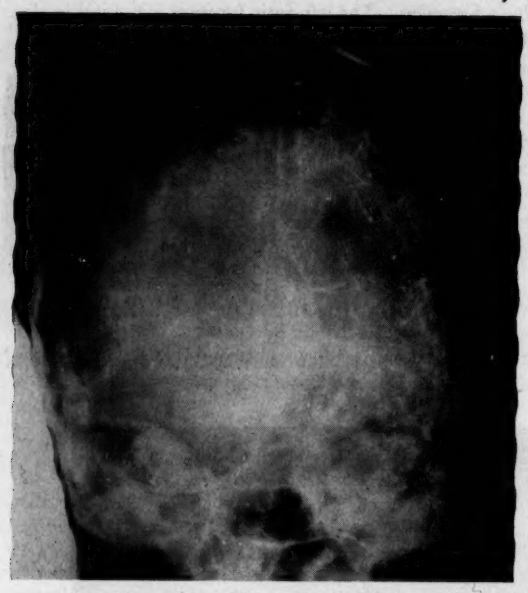

FIG. 8.—Arterial phase, antero-posterior view.

VENOUS PHASE.—The predominant drainage appears to be through the great vein of Galen, which is densely opacified, but the dye does not outline the transverse and sigmoid sinuses, probably because of the dilution of the dye at this stage (Fig. 9).

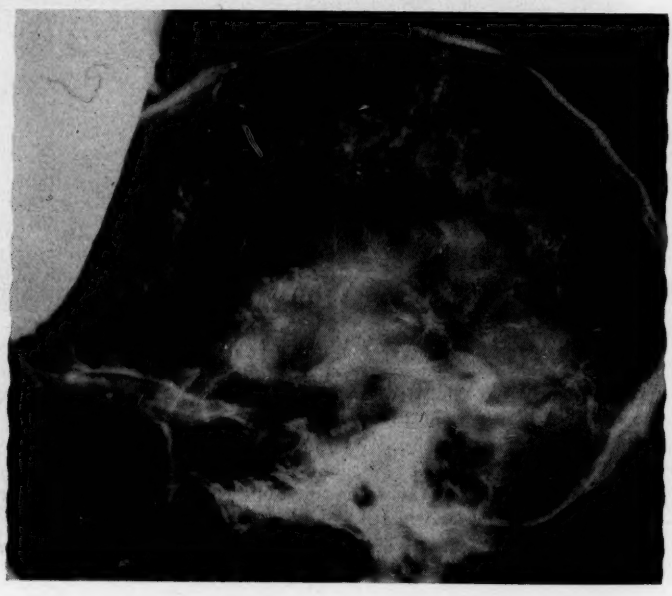

FIG. 9.—Venous phase, lateral view.

VENTRICULOGRAM.—This shows a general dilation of the lateral ventricles, the anterior, posterior, and temporal horns (Figs 10 and 11). Beneath this, but displaced upwards and backwards, is quite a large third ventricle, which is no doubt the site of a partial obstruction. There is no excess air over the surface of the hemispheres, which would suggest that the dilatation of the ventricles has not been produced by general atrophy, but rather by partial internal hydrocephalus due to pressure by the tumour. Also, although no good view has been obtained of the fourth ventricle, there is some basal air, which would indicate that the obstruction is certainly only partial.

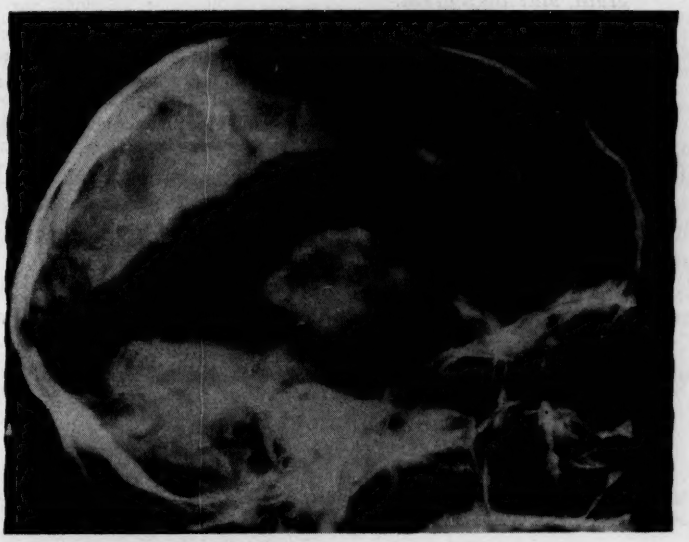

FIG. 10.—Ventriculogram, lateral view.

FIG. 11.—Ventriculogram, antero-posterior view.

SUMMARY

(1) The literature concerning congenital arterio-venous aneurysm of the retina has been reviewed.

(2) Observations have been made regarding its aetiology, the appearance of the retina, and the cause of the decreased visual acuity.

(3) An additional case is fully described, with fundus drawing, encephalogram, and angiogram.

I should like to thank Dr. A. D. D. Pye, Superintendent of the Brisbane General Hospital, for permission to publish the *x*-ray films, Dr. V. E. Sampson, who originally drew my attention to the case, Dr. John Nye, for the central nervous system examination, Dr. R. Row for the *x*-ray reports, Dr. J. Hart for helpful advice, Miss L. Pegus for the fundus drawing, and the Photographic Department of the University of Queensland for the other illustrations.

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Brit. J. Ophthal. (1958) **42**, 667.

STUDIES ON THE CORNEAL AND TRABECULAR ENDOTHELIUM

II. ENDOTHELIUM OF THE ZONE OF TRANSITION*

BY

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AT the periphery of the cornea the corneal endothelium passes over the margin of Descemet's membrane to the trabecular meshwork (Vrabec, 1957). The size and shape of the cells of the corneal endothelium undergo a peculiar change in approaching this region (Vrabec, 1958a). A study by means of the replica method (Vrabec, 1958b) demonstrated that the endothelial cells became elongated in the meridional direction and then lost their outlines in the region of the anterior border of Schwalbe's ring. Only a few nuclei were seen by the replica technique.

The results of examining the endothelium of this zone of transition by various methods is described below.

Material and Methods

The eyes of the cat, rabbit, and rhesus monkey were studied, together with some human eyes with different pathological conditions, and one human eye which was clinically normal but was enucleated because of an orbital tumour.

The basic method used was again the silver impregnation method of McGovern (1955, 1956). The results were compared with those obtained by the replica and pseudo-replica methods, the latter mostly with additional staining. Even in the apparently normal eye, the possibility of functional changes in the secretion of the cement substance as well as of the covering substance should be borne in mind. The specimens used were either frozen sections or teased preparations; most of them were mounted in Apáthy's syrup to prevent excessive dehydration and shrinkage of the cement substance; some specimens mounted in Canada balsam showed that the cement substance seems much more resistant to dehydration after impregnation with silver.

Findings

The cells of the corneal endothelium, as they approach the corneal margin, become elongated in the meridional direction and sometimes form fan-shaped groups. The shape and size of the cells as well as their outlines alter, and the endothelium shows a characteristic mosaic pattern. The cement substance often increases in thickness and sometimes covers the whole surface

* Received for publication September 30, 1957.

of the cell with a thin argyrophil layer. A sudden change occurs as the endothelium passes the border of Descemet's membrane; the cells become much larger and flatter, and their outlines become sinuous. In shape they resemble the endothelial lining of lymphatic vessels, as they have been so beautifully depicted by Jancsó. As it is advantageous to remove the iris and ciliary body before the silver impregnation, and since some superficial lamellae of the trabeculae are easily removed thereby, it is difficult to obtain satisfactory specimens of the zone of transition without losing the superficial endothelial layer. The following procedure therefore proved to be better. After the eye had been dissected into its anterior and posterior halves, the lens was taken from the anterior segment and the whole anterior segment was impregnated by McGovern's method. This impregnated anterior segment was then divided sagittally and each half was cut on the freezing microtome in the frontal direction. Large, flat, intact endothelial cells are often to be found in such specimens; their surface mostly bears a thin film of a slightly argyrophil granular substance. The cement substance usually shows irregular thickening and often extends in a thin layer over the surface of the cells. (Fig. 1, and Fig. 2 opposite).

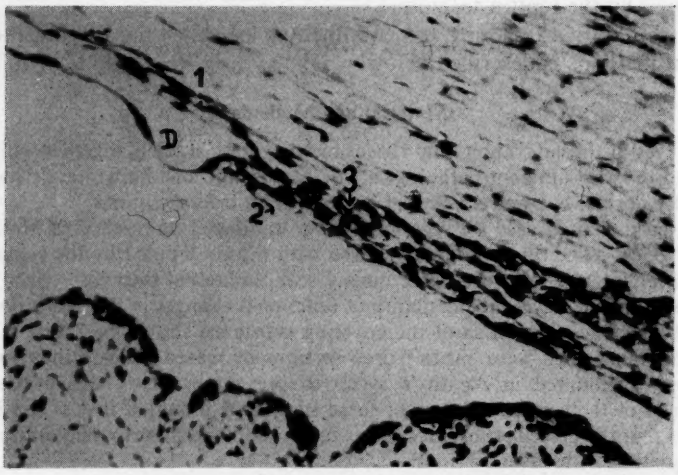

FIG. 1.—Sagittal section of anterior root of trabecular meshwork in the human eye, showing:
(D) Border of Descemet's membrane;
(1) Layers of anterior root of trabecula anterior to Descemet's membrane;
(2) and (3) Superficial and deeper layers of zone of transition.
Celodal embedding, impregnation by the Gros-Schulze method. × 366.

The endothelial layer passes more equatorially into the trabecular endothelium; its cells become elongated in various directions, and their outlines become irregular and even invisible. Simultaneously, a thin layer of granular amorphous substance (which does not take up silver or only does

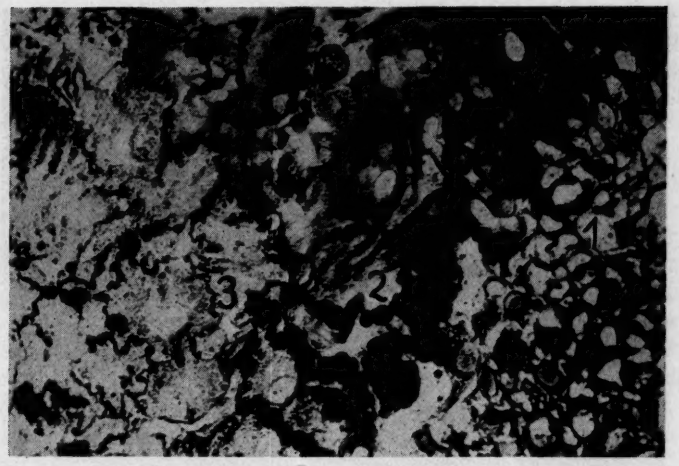

FIG. 2.—Endothelium of zone of transition in the human eye (zone 2 of Fig. 1), showing:
(1) Mosaic pattern of peripheral corneal endothelium;
(2) Increased covering substance, enlarged cell boundaries, and argyrophil ridges at beginning of zone of transition;
(3) Clearly outlined, large, flat endothelial cells of zone of transition.
The covering substance seems to have been removed in the dissection.
Flat-frozen section, after impregnation by McGovern's method. × 366.

so irregularly) appears on the surface of the trabecular meshwork. This layer conceals most of the details of the trabecular meshwork and is perhaps the cause of the poor results obtained with the impregnation method on the trabecular endothelium itself. The secretion of the covering substance is apparently similar to that of the corneal endothelium and is apt to spread over the whole cellular surface. Functional changes in this secretion would require further study; the present description refers to the superficial cellular layer covering the inner surface of the zone of transition in the region of the anterior border of Schwalbe's ring. By focusing the microscope somewhat below the margin of Descemet's membrane in the direction of the corneal stroma, other layers of nearly regular endothelial lining are seen to cover the few (three or four) sheaths which represent the anterior roots of the trabecular meshwork. There the trabecula is fixed into the corneal stroma anterior to Descemet's membrane. In meridional sections some rows of nuclei appear which are more numerous than in the neighbouring stroma. In flat-frozen sections, and even more frequently in teased preparations, it is possible to see islands of this endothelial layer with a regular endothelial lining surrounded by irregular scattered keratoblasts of the corneal stroma (Fig. 3, overleaf).

This is an interesting feature of the anterior roots of the trabecular meshwork. Consequently, the flat sheaths are covered by a regular and continuous endothelial layer. The cell outlines are very conspicuous and sometimes—

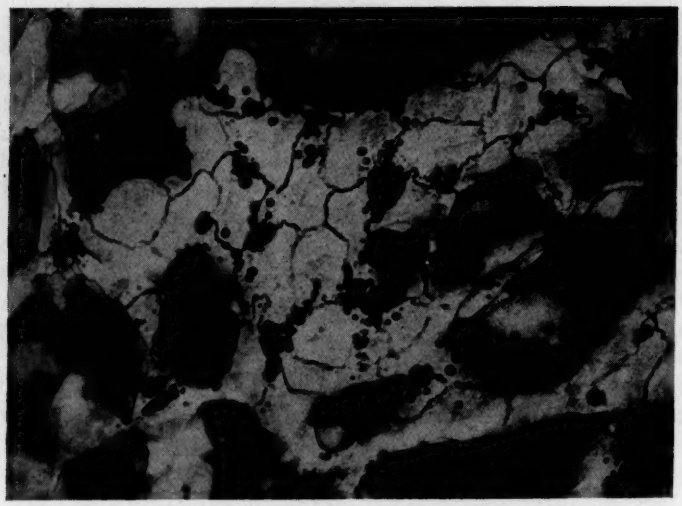

FIG. 3.—Anterior root of trabecula (Zone 1 of Fig. 1), showing islands of continuous layers of endothelium, cell outlines, and drop-like secretions of cement-substance. Flat-frozen section impregnated by McGovern's method. × 366.

especially near the border of Descemet's membrane—they appear to be irregularly thickened by the copiously secreted cement substance (Fig. 4).

FIG. 4.—Deeper layers of zone of transition in the human eye (Zone 3 in Fig. 1):
(1) Large irregular fields with unevenly thickened cell outlines, and irregular secretion of cement substance;
(2) Drop-like secretions of cement substance.
No cells are to be seen in this specimen. McGovern's method. × 666.

More posteriorly, approaching the trabecular meshwork itself, the endothelial elements undergo changes similar to those described for the superficial layer in the same region. The amount of the intercellular substance varies in a similar way; it frequently forms larger blocks apparently binding the sheaths of the anterior roots of the trabecular meshwork together into a compact structure analogous to the corneal stroma.

These observations support the findings of earlier workers that the anterior roots of the trabecular meshwork were built from solid sheaths. The islands of the continuous endothelial layer in the tangential frozen sections differ widely from the adjacent corneal stroma, in which keratoblasts are bound in a loose cellular network, large hyaline blocks of cement substance isolating single elements of the cell structure. The irregularity of the more posteriorly situated elements in the zone of transition is caused by the appearance of pores in the loose trabeculae. The appearances are so irregular that some doubts may arise regarding their cellular origin, but in the more heavily impregnated specimens some nuclei could be traced.

Phase-contrast microscopy demonstrated beautiful pictures of endothelial cells with their nuclei and Golgi meshes (Fig. 5). On the surface of such cells were seen drops of granular argyrophil substance, evidently identical with the cement substance. In the specimens stained with toluidine blue, this cement substance stained only faintly. The dilated cell outlines were connected in some places by large blocks of cement substance.

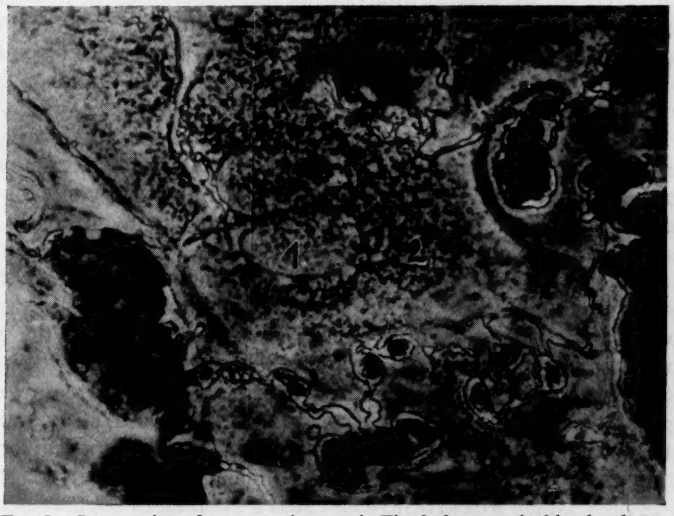

FIG. 5.—Same region of same specimen as in Fig. 3 photographed by the phase-contrast method, showing irregular outlines of one large field and drop-like secretions of cement substance. Within the outlines of a field is seen an endothelial element in the process of amitotic division. Nuclei (1) and Golgi meshes (2) are conspicuous.
The division of the cytoplasm is incomplete. McGovern's method. × 1,666.

Comment

The fan-shaped groups of endothelial elements at the periphery of the cornea were first noticed during studies on the relief of the inner surface of the structures surrounding the anterior chamber. As Descemet's membrane arises at a later stage of embryonic development than the trabecular meshwork and ciliary muscle, it is tempting to consider these groups in relation to the anterior anchorage of the ciliary muscle tendons (Kusel, 1906; Rohen, 1956). The elongation of the endothelial nuclei reported by Rochon-Duvigneaud (1892, 1893) in the periphery of the cornea seems to be related to the deformation of the whole cell-body.

The sudden increase in size of the endothelial elements at the edge of Descemet's membrane seems to arise from the flattening which was observed by early workers (Rochon-Duvigneaud, 1892, 1893; Kolmer, 1936) to be present in this region. In studying the endothelial covering of the anterior surface of the iris (Vrabec, 1952), I noted that the endothelial elements which pass from the cornea to the iris around the lateral wall of the anterior chamber at an early stage of embryonic development are distinctly thinner than the comparatively small corneal elements.

Previous authors who have studied the minute anatomy of the trabecular meshwork have thought that cell outlines could be demonstrated in the endothelial covering. In the superficial layer of the endothelium in the region of the anterior border of Schwalbe's ring as well as in the deeper three or four layers of the anterior roots of the trabeculae anterior to Descemet's membrane, however, the endothelial elements still preserve their distinct boundaries and form continuous layers. In the early stages of embryonic development, these elements form a compact wedge of uniform tissue in direct continuation of the corneal endothelium. Further differentiation takes place only in the posterior part of the trabecular meshwork, where mechanical and functional needs lead to the formation of a spongy tissue. The process seems to be linked to that observed in my study of evolution of the superficial layer of the iris. It corresponds to the involution of mesenchymal elements which takes place in the lateral wall of the anterior chamber during the second half of intra-uterine life. On the other hand, the persistence of continuous endothelial layers in the anterior roots of the trabecular meshwork also appears to be of functional importance. As the aqueous humour passes from the anterior chamber through the filter of the posterior trabeculae to Schlemm's canal, the spaces in the trabecular meshwork may enlarge, allowing the aqueous humour to reach the corneal stroma along the sheaths of the anterior roots of the trabeculae. It seems probable that, by secreting the cement substance, the endothelial cells actively control this aqueous flow, which would otherwise cause a swelling of the corneal stroma. Clemens (1955) mentions the importance of hyaluronic acid and its esters as well as of hyaluronidase in controlling the water-balance of the tissues. This finding appears to be related to the accumulation of an amorphous sub-

stance previously described (Vrabec, 1957), as well as to the deeper staining properties found in this part of the trabecular meshwork by Persson (1954).

Summary

The endothelial covering of the zone of transition in the region of the anterior border of Schwalbe's ring is described. Certain new aspects are considered from the morphological and physiological points of view. The peculiar fan-shaped groups of endothelial cells at the periphery of the cornea are closely related to the anterior anchorage of the ciliary muscle tendons. The endothelial elements immediately posterior to the margin of Descemet's membrane are conspicuously enlarged. The fact that the outlines of the cells are preserved in the endothelium of the zone of transition (in the superficial as well as in the deeper layers) may have some bearing on the control of the flow of aqueous humour to the corneal stroma through the sheaths of the trabecular meshwork.

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SECOND SEASON PREDNISONE TREATMENT IN VERNAL CONJUNCTIVITIS WITH SPECIAL REFERENCE TO CORNEAL COMPLICATIONS*

BY

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THIS work was started at the beginning of 1956, when a research clinic for vernal conjunctivitis was set up in the Hadassah University Hospital, Jerusalem. Many intractable cases from throughout the country were sent for consultation and this accounts for the high percentage of severe cases in the series; it also partly explains why so many serious corneal complications were seen in a relatively short period.

Classification of Patients

Of some 400 cases of vernal conjunctivitis seen in the clinic since the beginning of 1956, 100 were treated with prednisone.

Sufficient prednisone was not available for a longer series of cases, and those not so treated served as a control group.

Eighty-five of the cases receiving prednisone were classified as severe, and fifteen as moderate or mild. All the severe cases had some corneal involvement at one time or another. In most patients the disease was of the mixed variety, both palpebral and bulbar, but the presenting symptoms were due to the palpebral lesions in about two thirds of the cases.

The age and sex distribution of the hundred patients who received prednisone are given in Table I.

The duration of disease (Table I) varied from several weeks to 19 years (average 4 years).

TABLE I

AGE, SEX, AND DURATION OF DISEASE IN 100 PATIENTS

Age (yrs)		1–5	6–10	11–15	Over 16
No. of Patients	Total	9	30	32	29
	Male	7	23	24	22
	Female	2	7	8	7
Average Duration of Vernal Conjunctivitis (yrs)		2·7	3·4	3·3	5

* Received for publication December 9, 1957.

Previous Treatment

Most of the patients had already had various forms of treatment, including cortisone and hydrocortisone eye drops and ointment, local antibiotics, courses of desensitization injections, β-strontium irradiation, and surgery.

Patients were given prednisone instead of cortisone or hydrocortisone when these drugs were considered to be ineffective or not effective enough. It is worth while recording that some thirty patients gave a history of a good response to cortisone in the past, but with reduced benefit in the 1956 or 1957 season.

Methods of Treatment

Prednisone was given in the form of Metimyd eye drops (0·5 per cent. prednisone with 5 per cent. sulphacetamide: Schering) or Scherizolon (prednisone solution), diluted in saline to give a concentration of 0·25 per cent. The patients were asked to instil these drops three to five times daily initially, and less frequently as their condition improved.

Some patients were given additional Metimyd ointment for use before retiring at night.

25 very severe cases out of the 100 were also given courses of treatment with systemic prednisone. The initial dosage was 5 mg. three or four times daily, with a gradual decrease to a maintenance dose of 2·5 mg. three times daily for from 10 to 20 days. When necessary the course was repeated. We tried to prescribe this drug for short periods in the minimal effective dosage.

Duration of Treatment

The longest term of treatment was 1½ years and the shortest one month (average 6 months).

Sixty-five patients were started on prednisone therapy in 1956; fifteen of them have been under continuous treatment since then, receiving maintenance doses of Metimyd drops throughout the winter months. Thirty of the 65 patients were under treatment continuously during the summers of 1956 and 1957 and received no treatment during the winter months. In three cases in which treatment started in 1956, it was not necessary to continue treatment in 1957 because their clinical condition was satisfactory. The remaining seventeen patients did not reappear in the spring of 1957.

In 35 patients, prednisone treatment was commenced in the spring of 1957.

When prednisone therapy was started in 1956, thirty of the 65 patients were instructed to use Metimyd drops to the right eye and cortisone or hydrocortisone to the left eye. A week or 10 days later this order was reversed. However, as will be seen later, this procedure was soon stopped.

Cultures from the conjunctiva were taken from most cases and repeatedly from all cases suffering from corneal complications.

Results

The subjective criteria of effective treatment were taken to be diminution of irritation and of photophobia. The latter was usually one of the first

symptoms to disappear. Objective criteria were diminution in the amount of secretion and changes in the diseased conjunctiva. The palpebral vegetations lost their redness, and became pale and flatter, and in some cases completely disappeared within a few weeks. In bulbar cases the conjunctiva became white, and the limbal proliferations became flatter and in some cases eventually disappeared.

The Horner-Trantas spots usually disappeared in a few days and their continuance was considered an indication for increasing the dose of prednisone.

Of the corneal complications, the disappearance of superficial keratitis with its symptoms of photophobia and blepharospasm was a definite criterion as to the effect of therapy. The improvement in the corneal condition was sometimes noted within the first few days of treatment, even in patients who had been seriously disabled for weeks or months.

Most of these results could be obtained with local prednisone, but the more severe symptoms such as large limbal proliferations and torpid corneal ulcers could be more quickly controlled with systemic prednisone.

After intermission or cessation of treatment or when maintenance doses were inadequate, some relapses occurred. Resumption of or increase in dosage, however, soon brought the symptoms under control again.

Judging by these criteria, prednisone was superior to all other forms of therapy. Its superiority to cortisone and hydrocortisone was clearly brought out by the experiment in which thirty patients received prednisone to one eye and cortisone or hydrocortisone to the other eye.

In order to assess the relative value of cortisone and hydrocortisone as compared with prednisone in the management of vernal conjunctivitis, the results in the 100 cases treated with cortisone or hydrocortisone are compared with those in the 100 cases treated with prednisone (Table II).

TABLE II

COMPARATIVE EFFECTS OF CORTISONE, HYDROCORTISONE, AND PREDNISONE

Type of Response	Good	Medium	Little or None	Total
Cortisone and Hydrocortisone ..	8	36	56	100
Prednisone	100	0	0	100

Corneal Complications.—Of the 100 patients treated with prednisone five developed corneal ulcerations while under maintenance doses of Metimyd. The ulceration occurred from three to eight months after Metimyd was started. Fuller data relating to these five patients are given in Table III (opposite).

TABLE III

CLINICAL DATA RELATING TO CORNEAL ULCERATION IN FIVE PATIENTS

Case No.	Age (yrs)	Sex	Duration of Vernal Conjunctivitis (yrs)	Length of Prednisone Treatment (mths)	Site of Ulcer	Side
5	5	Male	4	3·5	Upper part of cornea	Right
49	8	Male	3	8	Upper part of cornea	Right
73	5	Female	4	5	Upper para-central	Left
178	5	Male	3	4	Upper part of cornea	Right
205	4	Male	3	3	Upper para-central	Both

All the above cases were under steroid therapy (cortisone and later prednisone) almost from the start of the disease. This serious complication occurred in small children only, and the age at onset was remarkably low. Reference to Table I shows that four out of nine in the 1 to 5-year-old age group developed corneal ulceration, whereas only one out of the remaining 91 patients of all other ages was affected in this way.

All the ulcers had a torpid course and did not respond to therapy unless prednisone was given orally, when healing progressed satisfactorily and was complete within a week or two.

In all five cases a nebula or macula remained at the site of the ulcer, and relapses at the same site or around it were common. Although there was only one bilateral case, the other cases showed a tendency to erosions in the second eye. The visual acuity was not appreciably affected, but there were 3 to 4 D astigmatism in two cases. All five children had either the palpebral or the mixed form of the disease. There was no trachoma in any of the five cases.

One patient only (Case 49) received β-strontium irradiations; the dosage, however, was small (3000 rep.) and the source was applied directly to the everted upper eyelid only. It is improbable that in this case these irradiations were the cause of the ulcer.

When the ulcerations appeared the vegetations on the conjunctiva of the upper eyelids were already so small and scarce that surgical intervention as advocated by Beigelman (1950) was not considered. In four cases the conjunctival cultures showed *Staphylococcus albus*, which was particularly sensitive to chloramphenicol; one culture was sterile. Treatment with chloramphenicol without systemic prednisone did not affect the ulceration.

Discussion

Of 48 cases treated with prednisone during two seasons, only three were considered to be cured, although in the seventeen patients treated by prednisone in the summer of 1956 who did not return in 1957 some cures may be assumed. The general impression is that the rate of cure in the group treated by prednisone was not greater than that to be naturally expected. Prednisone is probably the most effective drug at the present time in the management of vernal conjunctivitis, but there is no proof that it cures the disease.

The relation between steroid therapy and the apparent increase in frequency of corneal ulceration in vernal conjunctivitis requires further consideration. In our series five cases of corneal ulcer occurred while the patient was receiving prednisone. This may be unrelated to the therapy, and due rather to the fact that the prednisone-treated cases were nearly all severe. Prednisone by mouth quickly healed the corneal ulceration. Corneal ulceration also developed in a number of cases in which steroids other than prednisone were given, its incidence being proportional to the severity of the primary condition.

It is well known that corneal ulceration occurred as a complication of vernal conjunctivitis before steroid therapy was introduced. However, we were concerned with the possibility that prednisone might be more liable than cortisone to cause corneal ulceration. Of 300 cases of vernal conjunctivitis treated by cortisone, 2·66 per cent. developed corneal ulceration. The difference between this figure and the 5 per cent. found in the prednisone-treated group may be explained by the fact that the latter comprised more severe cases.

There was no evidence that infection played a part in the five cases of corneal ulceration described—a role which might conceivably have been attributed to the influence of steroids in lowering local resistance to infection. It is now our practice to give only systemic prednisone in cases of vernal conjunctivitis in which corneal ulceration has already appeared, though this may well be an unnecessary precaution.

Summary

(1) A hundred patients with vernal conjunctivitis received prednisone treatment, the majority during two consecutive years.

(2) The clinical data of these cases is supplied.

(3) During the same period 300 other cases of vernal conjunctivitis were treated without prednisone. These cases were used as controls.

(4) Prednisone was found to be superior to all other steroids in the management of vernal conjunctivitis.

(5) There is no evidence that it is effective in curing the disease.

(6) There is no conclusive evidence that it increases the liability to corneal ulceration, but, as a precautionary measure, the drug was given by mouth only in such cases. Further experience may show this precaution to be unnecessary.

The author wishes to express his indebtedness to Professor I. C. Michaelson, for his helpful advice and guidance throughout this work, which was supported by the Max and Rebecca Schrire Medical Research Fellowship. Messrs. Schering Corporation supplied the prednisone preparations used in the investigations.

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CHANGES IN OCULAR RIGIDITY IN ENDOCRINE EXOPHTHALMOS*

BY

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Two types of endocrine exophthalmos are frequently distinguished, being referred to thyrotoxic or hyperthyroid exophthalmos, and thyrotropic, ophthalmoplegic, or oedematous exophthalmos.

(*a*) *Hyperthyroid or Thyrotoxic Exophthalmos.*—This accompanies Graves's disease and is, therefore, much more frequently seen in females than in males. In the majority of cases the exophthalmos is quite unobtrusive or there is merely an appearance of exophthalmos due to retraction of the upper lid. It is associated with a decreased frequency of blinking and a fixed stare. The majority of authors agree that these symptoms should be attributed to an increase in tone of the sympathetic system. The importance of the pituitary thyrotropic hormone in this clinical picture is not clear. Hyperthyroid exophthalmos is not complicated either by chemosis or by diplopia, but heterophoria and lack of convergence are often seen.

(*b*) *Thyrotropic, Ophthalmoplegic, or Oedematous Exophthalmos.*—This may occur either in a subject suffering from verified and treated hyperthyroidism, when the signs of thyrotoxicosis are about to disappear, or in an apparently normal subject free from any thyroid symptom or history of symptoms. The second type is more frequently seen in males than in females.

Thyrotropic exophthalmos is often very marked and may even lead to irreducible lagophthalmos; it is invariably associated with a disturbance of ocular movements, particularly with elevation of the gaze. More or less marked chemosis sometimes complicates this condition. It is believed to be caused by the secretion of an exophthalmos-producing substance directly related to the thyrotropic hormone.

These two clinical entities, thyrotoxic and thyrotropic exophthalmos, may be encountered in the same subject. When a goitre is given treatment, a typical hyperthyroid type of exophthalmos is often seen to become more pronounced and to acquire the features of thyrotropic exophthalmos. Such transitions are so frequent that cases of either purely hyperthyroid or purely thyrotropic exophthalmos are relatively rare.

Albert (1945) discovered that exophthalmos could be induced in minnows by the injection of anterior pituitary extract. On the other hand, Dobyns

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and Wilson (1954) demonstrated that injection of serum from certain exophthalmic patients gives rise to ocular protrusion in the goldfish *Carassius auratus* (Japanese variety), whereas serum from other patients produced no such effect. This new test would seem to throw some light on the pathogenesis of endocrine exophthalmos.

This paper reports an attempt to reach an analogous goal using a different method. In a recent paper (Weekers and Lavergne, 1957), we have demonstrated that ocular rigidity is considerably reduced in thyrotropic exophthalmos but remains normal in thyrotoxic exophthalmos. Our observations at present cover a series of 26 cases of thyrotoxic and six cases of thyrotropic exophthalmos. Three of the latter cases were made available by Prof. J. François of Ghent, whose co-operation in this respect we gratefully acknowledge.

The techniques of determining the coefficient of rigidity (K) need not be described here, as they have been the subject of many previous publications (Friedenwald, 1937, 1954, 1957; Schmidt, 1956; Goldmann and Schmidt, 1957; Lavergne, Prijot, and Weekers, 1957).

The average ocular rigidity in normal subjects usually varies between 0·0200 and 0·0250, and it shows a somewhat wide margin of fluctuation in normal conditions, even in the absence of any anomaly of the eyeball (Table I).

TABLE I
FLUCTUATIONS IN OCULAR RIGIDITY (K) IN NORMAL SUBJECTS

Author	Date	Number of Cases	Average K (Ocular Rigidity)	Physiological Variation
Friedenwald	1937	500	0·0215	0·0060 to 0·0370
Schmidt	1956	—	0·0225	$s = 0·0089$
Personal Observations ..	1957	239	0·0246	$s = 0·0063$

Table II shows that in hyperthyroid subjects the ocular rigidity either remains normal or shows only very slight changes as long as the ocular affection retains the features of thyrotoxic exophthalmos as described, *i.e.* as long as there is no change in ocular motility and no chemosis.

TABLE II
FLUCTATIONS IN OCULAR RIGIDITY IN 26 CASES OF HYPERTHYROID EXOPHTHALMOS

Number of Eyes	K (Ocular Rigidity)		
	Minimum	Average	Maximum
52	0·0170	0·0226	0·0325

Table III, on the other hand, shows a marked decrease in ocular rigidity in six cases of thyrotropic exophthalmos with a change in ocular motility and chemosis.

TABLE III

DECREASE IN OCULAR RIGIDITY IN SIX PATIENTS WITH THYROTROPIC EXOPHTHALMOS

Number of Eyes	*K* (Ocular Rigidity)		
	Minimum	Average	Maximum
12	0·0080	0·0115	0·0150

Four of these patients were hyperthyroids, and were being treated either with radioactive iodine or with antithyroid substances. The other two patients showed thyrotropic exophthalmos without goitre or Graves's disease, and were receiving no treatment.

Chemosis seems to be the clinical symptom which heralds a decrease in ocular rigidity. This was normal in three cases of bilateral ophthalmoplegia of endocrine origin, which showed similarities to thyrotropic exophthalmos but lacked conjunctival oedema.

Apart from its value as an aid in diagnosing the nature of an endocrine exophthalmos, ocular rigidity is also of importance in the determination of the ocular tension. Endocrine exophthalmos—and particularly, or so it would seem to us, thyrotropic exophthalmos—is sometimes complicated by a pathological increase in ocular tension. The calibration tables of the Schiötz tonometer have been calculated on the basis of a rigidity of 0·0215. Tonometric determinations show certain errors when ocular rigidity is abnormally low. As a result, ocular hypertension is only too readily overlooked or underestimated in subjects with thyrotropic exophthalmos in whom ocular rigidity is decreased (Table IV, opposite).

Table IV shows the frequency of ocular hypertension in cases of thyrotropic exophthalmos. On the other hand, the ocular tension was normal in all cases of thyrotoxic exophthalmos included in this investigation.

The hypertension seen in thyrotropic exophthalmos shows varying degrees of intensity. In the majority of cases it is moderately marked and not associated with any change in the irido-corneal angle. In that case it develops parallel with the exophthalmos and recedes with its regression within a few months or years. It is favourably influenced by therapeutic measures which reduce the aqueous flow (Diamox or 2 per cent. adrenaline), but it improves only very slightly after treatment with miotics. However unobtrusive, it may give rise to glaucomatous defects in the field of vision (Figure, opposite).

TABLE IV

CORRECTION OF TONOMETRIC FINDINGS IN SIX SUBJECTS WITH THYROTROPIC EXOPHTHALMOS AND DECREASED OCULAR RIGIDITY

Eye	*K* (Ocular rigidity)	Ocular Tension (mm. Hg)		Difference (mm. Hg)
		Uncorrected	Corrected	
Right	0·0115	18·5	24	+5·5
Left	0·0100	20·5	26·5	+6
Right	0·0105	13	18·5	+5·5
Left	0·0105	12	18	+6
Right	0·0120	13	17·5	+4·5
Left	0·0140	16·5	20·5	+4
Right	0·0080	28	38	+10
Left	0·0125	21	27	+6
Right	0·0110	17·5	22·5	+5
Left	0·0140	17·5	21	+3·5
Right	0·0090	24·5	30·5	+6
Left	0·0150	23·5	26·5	+3

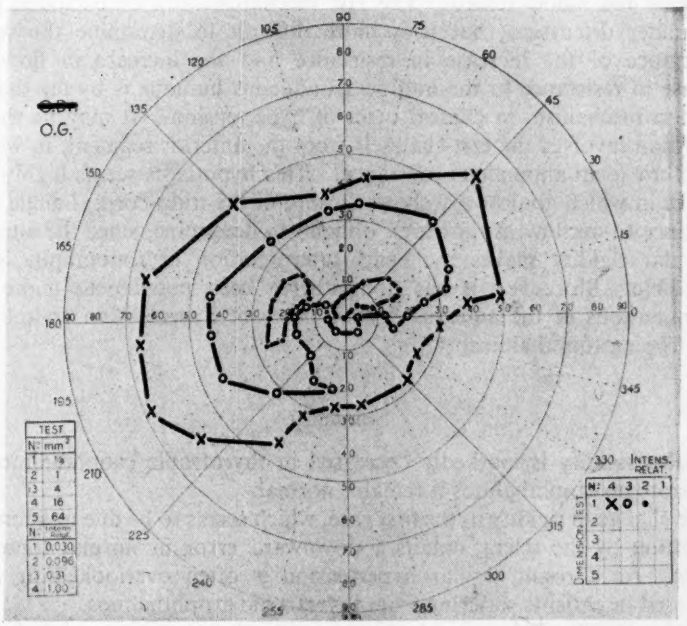

FIGURE.—Glaucomatous defects in thyrotropic exophthalmos complicated by ocular hypertension (left eye).

In rare cases hypertension may be manifested by an acute crisis, during which gonioscopy reveals closure of the irido-corneal angle. In such cases any medical treatment is ineffective, and an operation is required. In one of our cases the ocular tension did not become normal until one eye had been submitted to iridencleisis and the other to iridencleisis and angiodiathermy.

Comment

Thyrotropic exophthalmos is characterized by an increase in the water concentration of various tissues (Wybar, 1957). This phenomenon is seen in the orbit, the extrinsic muscles, and the subconjunctival spaces. It seems that the decrease in ocular rigidity revealed by differential tonometry is attributable to a change in the physical properties of the sclera, which results in an anomalous imbibition. To this phenomenon we may also attribute the abrupt changes in ocular refraction observed in one of our cases. Such changes in cases of exophthalmos with low ocular rigidity merit further investigation.

The pathogenesis of ocular hypertension in thyrotropic exophthalmos has so far remained obscure. It is known that any lasting increase is caused by an increased resistance to the outflow of aqueous humour, an increased flow, or an increase in venous episcleral pressure at the junction of the aqueous veins and blood vessels. The last mechanism can be excluded in the case under discussion, but it is more difficult to determine the relative importance of the increase in resistance and the increase in flow. An increase in resistance to the outflow of aqueous humour is by far the most common mechanism in clinical cases of hypertension. It may be that the imbibition involves the exit-channels from the anterior segment, in which it would create an anomalous resistance. This hypothesis seems highly likely in cases in which gonioscopy shows closure of the irido-corneal angle. The resistance to outflow, is, however, difficult to determine, since the alteration in ocular rigidity makes the exact interpretation of tonographic curves impossible. Moreover, it has not hitherto been possible to make exact determinations of the aqueous flow in cases of hypertension complicating thyrotropic exophthalmos.

Summary

Ocular rigidity is markedly decreased in thyrotropic exophthalmos, but in thyrotoxic exophthalmos it remains normal.

The change in rigidity in the first case, which seems to be due to anomalous imbibition by the sclera, entails a downward error in normal tonometric results. As a result, ocular hypertension is often overlooked or underestimated in patients suffering from thyrotropic exophthalmos.

The mechanism of ocular hypertension in thyrotropic exophthalmos remains obscure and merits further investigation.

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DIABETIC RETINOPATHY AND CYANCOBALAMIN (VITAMIN B_{12})*

A PRELIMINARY REPORT

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THE work of Ballantyne and Loewenstein (1943, 1944) served to clarify an understanding of diabetic retinopathy. Their findings have been amply substantiated by subsequent workers (Friedenwald, 1948; Ashton, 1950). A connexion between this condition and the Kimmelstiel-Wilson disease has also become established. More recently there is some evidence to implicate the adrenal cortex in the pathogenesis of the complex (Becker, 1952). Clinically, diabetic retinopathy and the Kimmelstiel-Wilson disease appear to be aggravated by the administration of ACTH in severe infections and during pregnancy: conditions which are all associated with increased adrenal cortical activity. Furthermore, the glomerular nodules typical of the Kimmelstiel-Wilson disease have been noted in rabbits after the administration of cortisone (Rich, Berthrong, and Bennett, 1950). In addition a relationship between vitamin B_{12}, diabetes, and the adrenal cortical hormones has been postulated (Becker, Lang, and Chow, 1953) and animals experimentally deficient in vitamin B_{12} have been reported to exhibit hyperglycaemia.

Skeggs, Nepple, Valentik, Huff, and Wright (1950), microbiologically measuring the amount of vitamin B_{12} in 8-hour urinary specimens obtained from diabetic patients who had been given an intramuscular injection of a test dose of 50 μg of vitamin B_{12}, found very marked excretory differences between patients with and without retinopathy. Compared with a normal non-diabetic value of 9·6 gamma excretion, 22 patients with retinopathy had an excretion average of 19 gamma; thirteen diabetics without retinopathy excreted an average of 4·2 gamma, and it is claimed that the marked difference in the fraction excreted provides a clinical test for the presence or absence of retinopathy in the diabetic. These findings are presumed to indicate an increased adrenal cortical activity in the presence of retinopathy.

Vitamin B_{12} has similarly been reported to be beneficial in the treatment of the diabetic neuropathies (Sancetta, Ayres, and Scott, 1951) and some interest has been taken in establishing a relationship between the presence of neuropathy and retinopathy in diabetics. It has been stated from the Johns Hopkins Hospital that over 90 per cent. of all diabetic neuropathies

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had, in addition, a retinopathy, and if vitamin B_{12} deficiency is responsible for the diabetic neuropathic condition it is perhaps permissible to postulate that the diabetic with retinopathy is also depleted of vitamin B_{12}, at any rate more so than the non-retinopathic diabetic.

It is conceivable that diabetes and adrenal cortical hormones act through a deficiency in vitamin B_{12} or through an inability to metabolize some steroids in the absence of B_{12}.

Becker, Allen, Winter, Maengwyn-Davies, and Friedenwald (1954) state that a deficiency of vitamin B_{12} is not in itself sufficient to produce diabetic retinopathy or Kimmelstiel-Wilson disease, because this vitamin failed to prevent the cortisone-induced renal lesion in experimental rabbits, some of the animals showing lesions despite massive doses of vitamin B_{12}. On the other hand, the incidence of cortisone-induced renal lesions in rabbits was markedly increased by the omission of vitamin B_{12} from their diet. The authors also state that severe deficiency of vitamin B_{12} in rats did not produce renal lesions comparable to those in the Kimmelstiel-Wilson disease. A diagnosis of the Kimmelstiel-Wilson syndrome outside the *post-mortem* room is largely clinical conjecture.

Chow, Rosen, and Lang (1954) compared the vitamin B_{12} serum levels in diabetic retinopathy and gave methods of estimating and determining the activity of B_{12} in serum. They summarized their findings by presenting data to demonstrate that the serum levels of B_{12} activity in diabetics with or without retinopathy are widely different, those in patients with retinal lesions being much higher than in patients without retinopathy. It seems clear that diabetics who have developed retinopathy handle their vitamin B_{12} quite differently from diabetics without retinopathy, who seem unable to retain the normal portion of a test dose of vitamin B_{12} and at the same time have higher levels of this vitamin in the peripheral blood. These workers think it impossible to escape the conclusion that vitamin B_{12} is somehow fundamentally involved in the pathogenesis of diabetic retinopathy. Injection of this vitamin in animals deficient of it is said to correct the hyperglycaemia produced by a glucose tolerance test.

It would, therefore, seem reasonable to treat diabetics who have retinopathy with large doses of vitamin B_{12}. This has been done and an interim report on the results is given herewith.

Method

From a large Diabetic Clinic a cross-section of controlled cases with retinal changes was selected, an attempt being made to include varying ages and differing degrees of retinal pathology. In each case a careful clinical examination of both fundi was carried out and a note was made of all changes present. Those findings which are believed to be common to both diabetic retinopathy and vascular hypertension, especially in elderly patients, were carefully recorded as were the findings which by common consent are alleged to indicate diabetes.

The fundi were classified in three groups:

(1) Minimal Diabetic Retinopathy.—Few haemorrhages and few small areas of exudate, with:

(*a*) Minimal hypertensive vascular changes;

(*b*) Moderate hypertensive vascular changes;

(*c*) Maximum hypertensive vascular changes.

(2) Moderate Diabetic Retinopathy.—More marked exudates, haemorrhage, and small central capillary aneurysms, with:

(*a*) Minimal hypertensive vascular changes;

(*b*) Moderate hypertensive vascular changes;

(*c*) Maximum hypertensive vascular changes.

(3) Marked Diabetic Retinopathy.—Severe haemorrhages and exudates (retinitis proliferans), with:

(*a*) Minimal hypertensive vascular changes;

(*b*) Moderate hypertensive vascular changes;

(*c*) Maximum hypertensive vascular changes.

The presence, or absence of any of the ocular complications associated with diabetes was noted. The systolic and diastolic pressure were measured and the age of the patient recorded. Blood sugar readings were taken and the presence or absence of glycosuria or acetonuria ascertained.

At the conclusion of these clinical recordings and before the administration of cyancobalamin, a selected number of patients had each fundus photographed in colour.

Test Cases.—Cyancobalamin was given intramuscularly daily for 14 days in doses of 1,000 μg. to ten selected patients. At the end of the course of treatment a further, similar clinical examination of each fundus was made, the details were recorded, and a second photograph in colour was taken. A third clinical examination was made up to 6 months after treatment. The particulars in the ten test cases are recorded in Table I (opposite).

Case Reports

Case 1, a male aged 44 years.—Diabetes discovered on routine examination in 1944.
Morning blood sugar 120 mg.
Blood pressure 140/90, stones in kidney.
Treatment by diet and insulin, soluble and clear.
Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 2*a*; after treatment, comparison of the coloured photographs showed in this particular case a marked lessening of the exudate on the temporal side (Figs 1 and 2, opposite). The haemorrhages appeared little changed. Examination of the fundi ophthalmoscopically showed similar improvement even 6 months after treatment.

TABLE I

TEN CASES OF CONTROLLED DIABETES TREATED WITH CYANCOBALAMIN

Case No.	Sex	Age (yrs)	Duration of Diabetes (yrs)	Blood Sugar (mg.)	Blood Pressure (mm. Hg)	Corrected Visual Acuity			
						Before Treatment		After Treatment	
						Right	Left	Right	Left
1	M	44	13	120	140/90	6/9	6/9	6/9	6/6
2	F	56	26	240	150/80	<6/60	<6/60	<6/60	<6/60
3	F	36	23	130	120/70	<6/60	1/60	<6/60	6/60
4	M	56	17	180 to 240	140/80	6/9	6/9	6/5	6/5
5	F	61	5	280 to 384	140/80	6/60	6/18	6/36	6/36
6	F	22	10	210	130/90	6/12	6/9	6/12	6/9
7	M	37	17	170 to 250	130/90	6/9	6/9	6/5	6/5
8	F	65	2	290	210/90	3/60	2/60	3/60	2/60
9	F	68	3	320	230/160	6/6	6/6	6/6	6/6
10	F	49	9	130	170/90	6/24	Counting fingers at 2 ft	6/24	6/60

FIG. 1.—Case 1, before treatment.

FIG. 2.—Case 1, after treatment.

Case 2, a female aged 56 years.—Diabetes discovered after the loss of a child 26 years previously.

Blood sugar 240 mg.

Blood pressure 150/80, blood urea 140 mg. per ml.

Treatment by diet and insulin.

Visual acuity < 6/60 in each eye.

Fundus Examination.—Before treatment, Group 3*c*; after treatment, very little change was noticed in the right eye, the degree of retinitis proliferans had increased in the left.

Case 3, a female aged 36 years.—Diabetes disclosed in 1934 by boils on the legs.
Blood sugar 130 mg.
Blood pressure 120/70.
Treatment by insulin.
Visual acuity < 6/60 in the right eye with cataract and 1/60 in the left.

Fundus Examination.—Before treatment, Group 3*a*; after treatment, condition unchanged.

Case 4, a male aged 56 years.—Diabetes discovered in 1940 on insurance examination.
Blood sugar 180 to 240 mg.
Blood pressure 140/80.
Treatment by diet and insulin lente.
Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 2*b*; after treatment, examination of the fundi photographs showed a lessening in the amount of retinal exudate in the central area. This lessening was more marked in the right eye than in the left. No other changes were noted. Clinical examination 6 months later showed this improvement to be maintained.

Case 5, a female aged 61 years.—Diabetes disclosed on the patient's complaint of loss of weight in 1952.
Blood sugar 280 to 384 mg.
Blood pressure 140/80.
Treatment by diet and insulin.
Visual acuity 6/60 in the right eye and 6/18 in the left.

Fundus Examination.—Before treatment, Group 3*b*; after treatment, both eyes showed haemorrhage and hard exudate, a typical text-book picture of diabetic retinopathy.

Case 6, a female aged 22 years.—Diabetes discovered 1947 at age of 12 years because of the patient's excessive thirst.
Blood sugar 210 mg.
Blood pressure 130/90.
Treatment by diet and insulin.
Visual acuity 6/12 in the right eye and 6/9 in the left, which showed early peripheral lens sclerosis.

Fundus Examination.—Before treatment, Group 2*a*; after treatment, the fundi seemed of better colour, but there appeared to be a few more haemorrhages on ophthalmoscopic examination. The exudates were unchanged.

Case 7, a male aged 37 years.—Diabetes discovered in 1940 at the time of an appendicectomy.
Blood sugar 170 to 250 mg.
Blood pressure 130/90.
Treatment by diet and insulin lente.
Visual acuity 6/9 in each eye.

Fundus Examination.—Before treatment, Group 3*a*; after treatment, clinically the right fundus seemed "drier", and the density and degree of exudate around the macula seemed less. The left eye showed very little change.

Case 8, a female aged 65 years.—Diabetes disclosed in 1955 by refractive changes.
Blood sugar 290 mg. Blood pressure 210/90.
Treatment by diet and insulin.
Visual acuity 3/60 in the right eye and 2/60 in the left; there were right lens changes.
Fundus Examination.—Before treatment, Group 1*c*; after treatment, unchanged.

Case 9, a female aged 68 years.—Diabetes disclosed in 1954 when the patient complained of pain in the legs and thirst.
Blood sugar 320 mg. Blood pressure 230/160.
Treatment by diet.
Visual acuity 6/6 in each eye.
Fundus Examination.—Before treatment, Group 2*b*; after treatment, unchanged.

Case 10, a female aged 49 years.—Diabetes disclosed in 1948 when the patient complained of loss of weight and skin irritation.
Blood sugar 130 mg.
Blood pressure 170/90. Neuropathy present.
Treatment by diet and insulin.
Visual acuity 6/24 in the right eye and counting fingers at 2 feet in the left.
Fundus Examination.—Before treatment, Group 3*a*; after treatment, more haemorrhages were visible below, but the degree of exudate was less on ophthalmoscopic examination though this was not seen in the photograph.

Controls.—A similar number of controls was selected and similarly examined (Table II). No vitamin B_{12} was administered and after a lapse of 6 months the cases were re-examined and the findings compared. Although many of the controls, judged by the blood sugar, appear to be severe diabetics, the Table shows that they were not necessarily severe cases of diabetic retinopathy.

TABLE II

TEN CONTROL SUBJECTS

Case No.	Sex	Age (yrs)	Duration of Diabetes (yrs)	Blood Sugar (mg.)	Blood Pressure (mm.Hg)	Corrected Visual Acuity Initial Reading		Fundus Group	Corrected Visual Acuity Final Reading	
						Right	Left		Right	Left
1	F	65	53	270	170/100	Hand movements	6/36	2*b*	Hand movements	6/60
2	F	24	1	290	120/90	6/24	6/18	1*a*	6/24	6/18
3	F	64	1	225	240/110	<6/60	6/60	2*c*	<6/60	Venous thrombosis
4	M	56	10	220	160/90	6/12	6/36	1*a*	6/9	6/24
5	F	65	3	180	250/120	<6/60	6/36	3*b*	6/60	6/36
6	F	57	5	190	145/95	6/18	<6/60	2*a*	6/18	6/60
7	F	28	2	150	130/100	6/24	6/24	2*a*	6/24	6/24
8	M	49	4	190	150/95	6/9	Perception of light	2*a*	6/9	Perception of light
9	F	63	9	200	190/110	6/24	Hand movements	2*b*	6/24	Hand movements
10	M	30	8	190	130/90	6/24 partly	6/60	2*a*	6/24	6/60

Results

The results of the investigation, while not impressive, showed that in Cases 1, 4, and 7 the degree of exudate in the retina was less after treatment than before as judged by both ophthalmoscopic examination and by fundus photography (Table III).

TABLE III
COMPARISON OF CLINICAL FINDINGS (CONTROLS)

Case No.	Initial Examination		Final Examination	
	Right Eye	Left Eye	Right Eye	Left Eye
1	Exudates, haemorrhages	Exudates, haemorrhages, synechiae	Unchanged	Unchanged
2	Fundus clear	Hard exudates on temporal side	One or two tiny round haemorrhages, few pinpoints of exudate on temporal side	Unchanged
3	Senile lens changes, flame-shaped and round haemorrhages, one or two aneurysms and areas of exudate	Senile lens changes, many flame-shaped haemorrhages, exudate	Unchanged	Venous thrombosis
4	Hard exudates in paramacular area	Exudates in central area	Micro-aneurysms below the disc	Unchanged
5	Masses of hard exudate in central area, small round haemorrhages throughout, senile lens changes	Hypertensive retinopathy	Unchanged	Unchanged
6	Lens spikes, hard exudates in centre of fundus, few haemorrhages	Masses of exudates below the macula	Increase of exudate and haemorrhages	Increase of exudate, haemorrhages present
7	Exudates and haemorrhages scattered throughout	Central exudate and haemorrhages	Unchanged	Unchanged
8	Nasal side of disc showed tiny aneurysms, about eight in number, "bunch of grapes" formation	Central choroidal sclerosis, aneurysm below macular area	Unchanged	Unchanged
9	Aphakia Haemorrhages and exudates in macular area	Cataract	Unchanged	Unchanged
10	Small haemorrhages and exudate in centre of fundus	Early peripheral lens changes, one or two tiny round haemorrhages in centre	Unchanged	Retinal oedema

No similar lessening of exudate was noticed in any of the controls. This improvement has maintained for up to 6 months in some cases. While it is agreed that the exudates in any form of exudative retinitis tend to lessen, particularly after the "peak period" of the condition is passed, it is perhaps a little significant that in one or two cases in the series this took place within a definite period and under similar conditions.

Lederer, Brichant, and Brichant-Doyen (1955) were of the opinion that the administration of vitamin B_{12} to diabetics with retinopathy increased the capillary resistance. No significant lessening of superficial or deep haemorrhages was noted in the majority of cases of this series.

Summary

Ten cases of diabetic retinopathy were ophthalmoscopically examined before and after a course of treatment with intramuscular cyancobalamin (vitamin B_{12}) in doses of 1,000 μg. daily for 14 days. Selected cases had coloured fundus photographs taken before and after treatment. An equal number of controls was similarly examined and reported upon.

It was noted on comparing the photographs before and after treatment that in three cases the degree of retinal exudate had diminished.

Of the ten cases clinically examined five had improved; of this number two cases were in Group 2*a*, which was considered the most important, one in Group 2*b*, and two in Group 3*a*.

Of the controls the condition in five cases was unchanged except for variations in visual acuity. In all the remaining five the condition had deteriorated in one or other eye.

We are indebted to Dr. W. P. Kennedy, F.R.S.Ed., Chief Medical Officer to the Distillers Company (Biochemicals) Limited, and to that Company for the supply of cyancobalamin; to the physicians of St. Helier Hospital for permission to use their cases and in particular to Dr. C. Hirson for his help. We are also grateful to Dr. Peter Hansell, Director of the Medical Illustration Department of the Institute of Ophthalmology, for the fundus photographs.

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HEREDITARY CILIARY AND SUPERCILIARY HYPOTRICHOSIS OF A DOMINANT CHARACTER*

BY

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CONGENITAL lack of lashes and eyebrows, whether total or partial, is seldom encountered. Associated at times with other developmental defects, mostly ectodermal, it may appear in conjunction with general alopecia, faulty dentition, and/or cataract formation (Duke-Elder, 1952). In the so-called Ullrich-Dohna syndrome, it has been seen in combination with multiple ocular malformations, strabismus, micrognathia, trigonocephaly, and hypogenitalism (Ullrich and Fremerey-Dohna, 1953; Weyers, 1954; Leffertstra, 1956); the disease is not hereditary. In one instance, at least, it has also been observed as part of a complex syndrome consisting of retinitis pigmentosa, opacities of the lens, anisocoria, oligophrenia, and some degree of somatic hypotrophy (Sánchez Salorio, 1955); the affection was transmitted according to a simple recessive pattern.

Its early occurrence in cases of hyperkeratosis follicularis spinulosa decalvans (Siemens, 1926) has likewise been recorded (Wessely, 1929); in this condition, which shows a sex-linked recessive mode of inheritance (Holthuis, 1943; Jonkers, 1950), fine, superficial punctate opacities of the cornea have been described, which, according to Franceschetti, Rossano, and Jadassohn (1956), Franceschetti, Jaccottet, and Jadassohn (1957), and Sendi (1957), occur primarily and not as a consequence of the scarcity of cilia.

As an almost isolated anomaly, ciliary alopecia is still less common, since, as far as we know, it has been observed but once (Traquair, 1912), in a father and son, in whom not only the eyelashes but the intermarginal area of the lower lid was absent.

On account of its considerable rarity, we feel justified in presenting the pedigree of a family in which the defect was strictly localized to the eyebrows and lashes and appeared in three generations (Figure). All the members of this family except the affected subject in the first generation were seen personally.

Case Reports

Case 1 (III, 4), an alert and well-developed 17-year-old girl, was said to have almost completely lacked cilia and brows from birth. She had had good vision until recently, when some difficulty in perceiving distant objects had been noticed.

* Received for publication December 24, 1957.

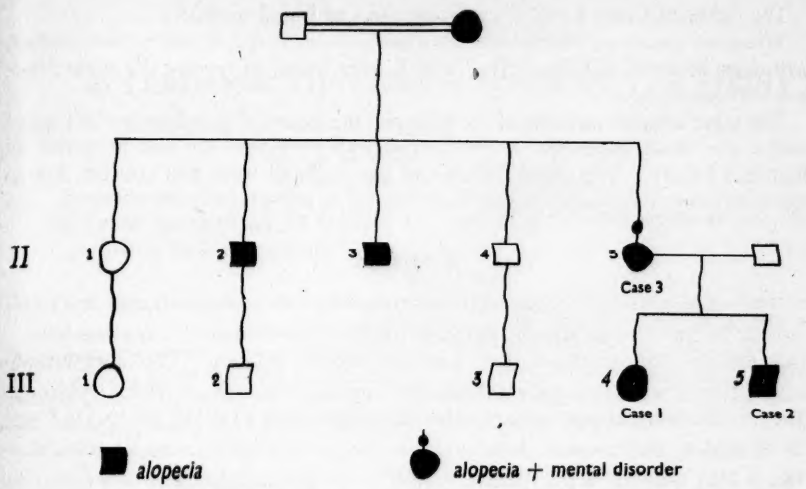

FIG.—Pedigree showing dominant inheritance of congenital lack of cilia and supercilia in three generations.

On examination, no lashes proper, but only scanty, extremely fine, downy, blond hairs were present at the upper lid margin; on the lower lid even these lanugo-like, rudimentary cilia were completely absent, but the margins were normal in all other respects. The eyebrows were also almost entirely missing, but the scalp exhibited a luxuriant hair growth, brown-black in colour, as did the other normally hairy parts of the body.

The eyes and their adnexa were otherwise normal. The visual acuity was 20/20 in each eye with correction −4·5 D sph., −2 D cyl., axis 0° in the right eye, and −3·5 D sph., −2·5 D cyl., axis 5° in the left.

No other physical abnormalities were present.

Inasmuch as the defect appeared to be due to a germinal disturbance, the patient's relatives were traced in order to establish whether it was sporadic or hereditary.

Case 2 (III, 5), a 15-year-old boy, younger brother of Case 1, in whom the eyebrows and lashes had always been absent, had complained of poor distant vision since the age of 13. The clinical picture was exactly the same as in Case 1. In addition, a moderate degree of acne vulgaris was present on the face, back, and chest; no signs of hyperkeratosis follicularis were detected.

The visual acuity was 20/20 in each eye with correction −1·75 D sph.

Case 3 (II, 5), a 39-year-old woman, mother of Cases 1 and 2, gave a similar history of congenital lack of lashes and eyebrows and of some shortsightedness since puberty. She had been afflicted for the last few months with involutional melancholia and had entered a mental home.

The anomaly in this case was identical in all respects with that in the children. The media and fundi were normal, and, although the refraction could not be adequately determined, it was ascertained that a myopia of 2–3 D existed, because the retina could be seen clearly only by the interposition of such a concave lens.

No skin disorders nor other physical anomalies were present.

The father of Cases 1 and 2 was examined and found normal.

When the remaining sibs in the second generation (II, 1, 2, 3, and 4) were studied, two elder brothers of Case 3 (II, 2 and 3) were found to present the same defect but without myopia.

The other affected member of the pedigree, the maternal grandmother of Cases 1 and 2 was dead, but it was satisfactorily established that she had presented an identical picture. The grandmother and her husband were first cousins, but no information concerning her brothers and sisters or parents could be obtained.

Comment

The occurrence of congenital underdevelopment of the lashes and eyebrows in three generations makes it highly improbable—to say the least—that the anomaly might be due to environmental factors. The facts demonstrate that it is a genetically determined, regularly dominant trait. Although the simultaneous appearance of other disorders, such as slight myopia in Cases 1, 2, and 3, and mental deficiency or disease in Case 3, may be coincidental, it may indicate a polyphenic action of the pathogenic gene or a disturbed genotypic milieu.

Summary

A pedigree showing the transmission of a hereditary, dominant type of congenital ciliary and superciliary hypotrichosis is presented.

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Brit. J. Ophthal. (1958) 42, 697.

CASE NOTES

SCLEROSING LIPO-GRANULOMA IN THE ORBIT*

BY

G. B. DAVIES AND P. L. WONG

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THIS case is reported as a mass in the lower lid presumed to be due to "sclerosing lipo-granuloma".

Case Report

A boy aged 16 years reported at the Surbiton Branch of the Royal Eye Hospital on December 29, 1956, complaining of a painless swelling in his left lower lid which had appeared gradually during the past 7 days. He had received a light blow from a fist on his left eye while "fooling around with a friend" about 4 weeks previously, *i.e.* in the first week of December. The swelling had subsided uneventfully in the course of a week to 10 days, but 7 days before attending hospital it had re-appeared and had gradually become larger. There was no pain, tenderness, lacrimation, diplopia, or enlargement on sneezing or coughing.

Examination.—The visual acuity was 6/9 unaided in the right eye and 6/9 less 2 unaided in the left eye. The mass involved the entire width of the lower lid and extended to an inch below the lid margin. It was firm in consistency, although rather irregularly so, as if there were calcareous nodules in it. There was no tenderness on firm pressure, no fluctuation, and no transillumination. The skin was bound down to the mass which could not be distinguished from the orbital margin, nor moved away from it. There was some chemosis of the bulbar conjunctiva at the outer angle and some oedema of the upper lid. The pre-auricular lymph node was not palpable.

There was no proptosis, and no limitation of ocular movement. The eye was quiet and the fundus appearance normal.

X ray of the left orbit revealed no bony injury and no bony deposits in the left lower lid.

Diagnosis, Treatment, and Progress.—A provisional diagnosis of unresolved haematoma with renewed bleeding was made, and a subcutaneous injection of 1,000 units hyaluronidase in 1 ml. distilled water was given into the mass through the skin. The swelling partly subsided during the next few days.

By January 14, 1957, the swelling had become appreciably larger. There was slight proptosis and limitation of action of the inferior rectus muscle presumably caused mechanically by the pressure of the mass. The visual acuity in the left eye was recorded as 6/12. There was no pyrexia and no tenderness.

On January 19, 1957, the swelling had still further increased in size and was causing considerable displacement upwards and a little outwards. Eye movements were limited in all directions, there was more chemosis, the left upper lid was more oedematous, and a mass not previously noted was palpable in the outer corner of the left upper lid. This was also firm but differed from the mass in the lower lid in having well-defined edges; it was not attached to skin and was freely movable over the orbital margin. There was no palpable isthmus between this and the larger mass. No pre-auricular adenopathy was found, but the left tonsillar lymph gland was palpable.

The patient was admitted to hospital for further investigations and observation. General examination revealed an asthenic build with pigeon chest and lumbar kyphosis. There were small palpable axillary lymph nodes, but no lesions were found in the circulatory, respiratory, or cardiovascular systems. The blood pressure was 120/80.

* Received for publication October 23, 1957.

Laboratory Investigations.—Erythrocyte sedimentation rate 15 mm. in 1 hr (Wintrobe); haemoglobin 96 per cent. (Haldane) equivalent to 14·2 g.; white blood count: 6,800 per c.mm., neutrophils 58, lymphocytes 38, monocytes 2, eosinophils 2, Wassermann reaction, Kahn test, and gonococcal complement-fixation tests were all negative; bleeding time 1 min. 25 sec., clotting time 4 min. 15 sec.

A second *x* ray taken some 3 weeks after the first showed no abnormality in the orbit. There was no calcification in the lower lid, no evidence of sinus infection, and no bony abnormality. The left sphenoidal fissure was a little wider than the right. No pulmonary lesion was seen in the chest *x* ray. A consultant E.N.T. surgeon reported no abnormality in the patient's nose or sinuses.

A search for actinomyces in the material removed from some superficial sebaceous cysts near the edge of the mass proved negative, and a culture of this material isolated *Staphylococcus aureus.*

Meanwhile, the patient was treated with systemic penicillin and sulphadimidine, in case the mass had originated from some deep-seated suppuration.

As investigations proved inconclusive, he was submitted to biopsy to exclude a possible rhabdomyosarcoma.

Dr. M. Lederman of the Royal Marsden Hospital very kindly arranged for biopsy to be performed at that hospital. Two pieces were removed for section, one from the swelling in the lower part of the orbit through the lower lid itself, and the other from the upper and outer part of the left orbit.

Dr. D. Gowing, Pathologist at the Royal Marsden Hospital, reported as follows:

"Two specimens were received. Microscopical examination shows similar features in both. There are many large fat vacuoles with surrounding groups of histiocytes and giant cells. Dense fibrosis is present, the fibrous tissue being infiltrated with lymphocytes, plasma cells and a few polymorphs. The appearances are those of a granuloma following traumatic fat necrosis ("sclerosing lipo-granuloma"). There is no evidence of new growth."

Prof. Norman Ashton, of the Department of Pathology, Institute of Ophthalmology, kindly reported on a biopsy specimen sent to him by Dr. Lederman, and confirmed the diagnosis of "sclerosing lipo-granuloma", the report being as follows:

"Section shows a mass of dense fibrous tissue containing numerous fat spaces surrounded by two sharply demarcated zones; an inner one of the macrophages and foreign body giant cells, and an outer one of loose relatively cellular fibrous tissue. The remainder of the mass is infiltrated both focally and diffusely with inflammatory cells of all types. The histological picture is typical of sclerosing lipo-granuloma."

Photographs showing macroscopic and microscopic features of the mass were also prepared by Prof. Ashton (Figs 1–4).

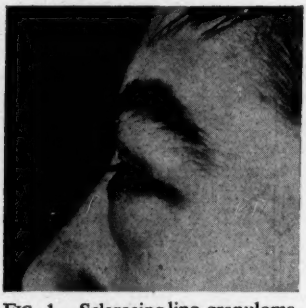

FIG. 1.—Sclerosing lipo-granuloma in upper and lower lids, showing extent of swelling due to underlying mass.

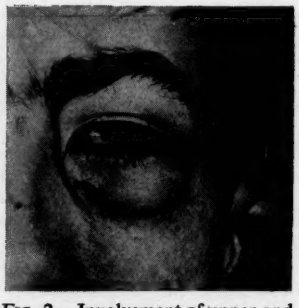

FIG. 2.—Involvement of upper and lower lids by sclerosing lipo-granuloma.

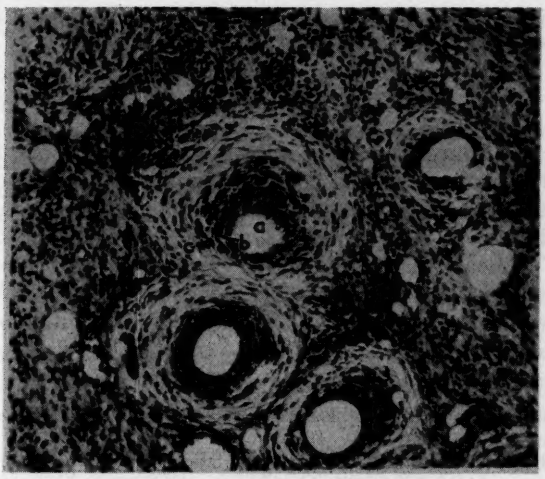

FIG. 3.—Typical histological appearance of sclerosing lipo-granuloma, showing infiltration with inflammatory cells of all types. × 90.
(*a*) Fat spaces
(*b*) Macrophages and foreign body giant cells
(*c*) Loose, relatively cellular fibrous tissues.

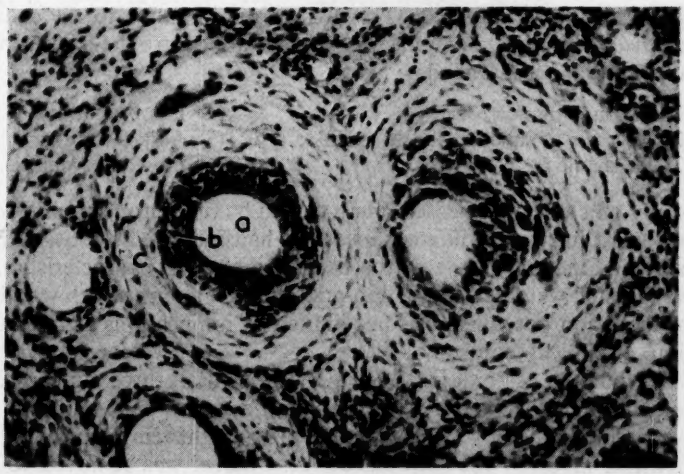

FIG. 4.—High-power photomicrograph, showing same features as Fig. 3. × 200.

Result.—Subsidence of the chemosis and oedema of the eyelids, which had begun 2 days before biopsy, continued after the biopsy was performed, and all treatment was discontinued when the pathological diagnosis was known. The patient was discharged on February 9, 1957, and one week later the visual acuity in the left eye was 6/6, and the swelling was appreciably smaller and softer. There were no symptoms, and the patient returned to work.

On March 23, 1957, the swelling appeared unchanged, and treatment with potassium iodide 10 gr. was started to see its effect on the course of the swelling.

Discussion

In a review of fourteen cases of sclerosing lipo-granuloma, Smetana and Bernhard (1950) discussed this condition as a pathological entity. They recognized that a peculiar granulomatous reaction which occurred in subcutaneous fat tissues after injury of various types had long attracted the attention of clinicians and pathologists. Differences in behaviour, course, and significance have led to the recognition of several clinical entities and syndromes within the large and ill-defined group of conditions characterized by the reaction:

(1) Traumatic fat necrosis of the female breast;
(2) Relapsing febrile non-suppurative nodular panniculitis, or Weber-Christian disease;
(3) Adiponecrosis subcutanea neonatorum and calcinosis;
(4) Changes in the lung parenchyma after the aspiration of oils and fats.

Even after the separation of these recognized entities, there remained a large number of cases characterized by a granulomatous reaction in the subcutaneous fat tissue of essentially uniform histological appearance, but attributed to different causes. The many names applied to the conditions characterized by this reaction, which have added to the confusion and difficulty of diagnosis, include:

(1) Saponifying necrosis;
(2) Necrosis of subcutaneous fat tissue;
(3) Ischaemic fat necrosis;
(4) Lipo-granuloma;
(5) Adiponecrosis;
(6) Lipoid necrobiosis.

A study of a number of cases characterized by tumourous swelling of subcutaneous fat in several different locations had indicated the desirability of choosing a name descriptive of the basic pathological characteristics. The name suggested was "sclerosing lipo-granuloma", a term which was descriptive of the lesion but which was not limited by implications as to causation, location, or clinical features.

Of the fourteen cases described, nine were genital, three gluteal, one was in the arm, and one in the orbit. The patient with this condition in the orbit first complained of a small pimple in the right temporal region. The mass, which involved the retrobulbar fatty tissue, was removed to relieve pressure on the eye, and the diagnosis was made on histological examination. No history of trauma was given.

Pincus (1935) mentioned a case presenting with recurrent abscesses of the eyelids, finally resulting in a fistula and pressure on the eye causing blindness. There was no history of trauma, and the diagnosis was made on histological examination after partial exenteration.

Reese (1951), discussing chronic granulomata of the orbit, reported a case due to fat necrosis, presenting as a localized tumour-like mass in the eyelid, that appeared spontaneously without any known cause. There was again no history of trauma.

Smetana and Bernhard (1950) came to the conclusion that the only treatment known to influence the course of sclerosing lipo-granuloma is the complete surgical removal of the tissue involved.

The progress of the swelling in the present case, which has been treated conservatively, will be kept under observation.

Summary

A case is described of an orbital swelling which was diagnosed on biopsy as a sclerosing lipo-granuloma, a form of fat necrosis with granulomatous reaction. A definite history of trauma was given.

We are grateful to Mr. T. M. Tyrell for permission to report this case, and to Mr. A. J. Cameron, Dr. M. Lederman, Prof. Norman Ashton for their interest, advice, and help.

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Brit. J. Ophthal. (1958) **42**, 702.

MACULAR LESION AFTER INFLUENZA*

BY

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VARIOUS ocular complications have been reported in influenza, including optic neuritis, iridocyclitis, interstitial keratitis, marginal corneal ulcers, and dacryoadenitis. The following patient showed macular lesions in both eyes after an attack of influenza during the epidemic of June, 1957. The condition is thought to be rare enough to be worth reporting.

Case Report

A Hindu woman aged 25 came to hospital complaining of diminution of vision in both eyes after an attack of influenza in June, 1957. The attack had lasted for 7 days, with sudden onset of racking headache, aching pain in the loins and limbs, distressing dry cough, and a few erythematous spots. The temperature rose to 104°F. for 3 days with marked prostration, and the eyes were red and inflamed. The patient was treated with aspirin and chloramphenicol, no respiratory complications occurred, and recovery was uneventful.

As soon as the attack had passed off the patient noted a marked diminution of vision for distant objects. She was at the time in the sixth month of pregnancy and in due course gave birth to a normal baby.

Examination.—She was somewhat obese with no local or general disease. The visual acuity was 6/36 in both eyes. Refraction was +1·5D sph. The media were clear. The fundus showed shining vesicular dots, three in the right eye and four in the left, round about the macula with a capillary ending at each one of them. The foveal reflex was absent. There was irregularity of the macular region, and, although no discrete pigment deposits could be made out, the whole area was somewhat darker than normal.

The visual acuity could not be improved by glasses.

The heart and lungs showed no complications of influenza.

Discussion

The macular lesions seemed to be of vascular origin. Phlebitis is not a rare event in the course of this disease and may result in petechial haemorrhages anywhere in the body. That this occurred in this case is evidenced by the appearance of erythematous spots on the limbus during the attack. Probably the macular lesion was of the same aetiology and was due to involvement of the retinal and choroidal vessels.

This case was seen at the Victoria Hospital, Baratpur, Rajasthan, and I should like to thank Dr. T. G. Mathur, Principal Medical and Health Officer, for permission to publish it.

* Received for publication January 6, 1958.

Brit. J. Ophthal. (1958) **42**, 703.

CORRESPONDENCE

REMOVAL OF CORNEO-SCLERAL SUTURES

To the Editorial Committee of the BRITISH JOURNAL OF OPHTHALMOLOGY

SIRS,—I am grateful to Mr. H. B. Stallard for his interest in my short contribution on the removal of corneal sutures and for his apt comments. I ought to mention that the object was to draw attention to certain advantages in using a knife and not to convey that the procedure was one of my own invention; indeed I learnt the method from my colleague, Mr. J. Sherne.

> The thing that hath been is that which shall be, and that which is done is that which shall be done: and there is no new thing under the sun. Is there anything whereof it may be said 'See this is new?' It hath been already of old time, which was before us. *Ecclesiastes*, **1**, *ix* and *x*.

I confess I did not know that Mr. Stallard had been using a knife, but I am pleased to hear that he does so with success.

I am, Sirs,
your obedient servant,
PETER WILSON.

32 PARK SQUARE,
LEEDS, 1.
September 6, 1958.

REFERENCES

STALLARD, H. B. (1958). *Brit. J. Ophthal.*, **42**, 507.
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BOOK REVIEWS

Refraction of the Eye and its Anomalies. (La refraccion del ojo y sus anomalias.) By E. GIL DEL RIO. 1957. Pp. 592, 335 figs, bibl. Tip. Cat. Casals, Barcelona.

The author's object is to correlate theoretical conclusions regarding accommodation with clinical findings so as to make the book available to a wide circle of readers. The approach is encyclopaedic: the introductory chapters cover the history, not only of the study of accommodation, but also that of light, and there are references to subjects as far apart as the crystal lenses of Niniveh and the Compton Effect encountered in nuclear physics. There is a simple but sound chapter on the elements of physical optics, simplified treatments of prisms, simple and compound lenses, and their aberrations. This is followed by a brief chapter on ocular anatomy (which contains a charming "open eye" diagram). Theories of accommodation are reviewed, particular attention being paid later to measuring techniques. Chapter 13, which deals with subjective procedures of measuring ocular refraction, is, in many ways, the most instructive of all, because it contains a succinct description of material usually flung far apart. Numerous clinical aspects are considered in detail, special attention being given to new developments in contact lens technique.

One or two minor criticisms have to be put on record. The references give a somewhat erratic impression. Only some of the authors are believed to have first names, their surnames are frequently mis-spelled both in the text and in the bibliography, and one French authority is referred to with profound respect although he has never done any work on ocular refraction and produced only one study on visual physiology. The illustrations are not uniform in quality. On the whole, however, the book can be recommended as useful.

Psychosomatic Ophthalmology. By T. F. SCHLAEGAL, with the collaboration of M. HOYT. 1957. Pp. x +502. Baillière, Tindall, and Cox, London. (88s.)

Stress and emotional upset are present at some time in the lives of most people. By maintaining that nervous and vascular disturbances, causing a whole host of pathological changes, may follow, the authors advance a theory which is very difficult to refute but which one knows, instinctively, to be spurious in very many cases. There are few diseases in which this argument is not used; sometimes it is sexual guilt, sometimes financial, marital, or business worry which causes the stress.

To equate the cornea with the hymen and corneal damage with defloration, is a little farther than most oculists in Great Britain would be prepared to go, and statements like this tend to cause a slightly uncomfortable feeling. Perhaps this would be interpreted as due to subconscious guilt. It appears that any improvement after the removal of a focus of infection is caused by subconsciously regarding such surgical intervention as symbolic of castration and the expiation of guilt.

That a detachment of the retina was replaced, after an unsuccessful operation, by a solution of the patients' home problems makes one pause, and that cataract may be due to guilt is no less startling. Pulmonary tubercle can, apparently, be caused by repressed sexual feelings.

Here and there one can subscribe to the authors' *dicta*—as, for example, in the management of dyslexia in children, how to tell a patient he has cataract, how to manage an adult before, during, and after operation, in the attitude of sighted people towards the blind, in the reaction of the patient to recent blindness, and in the treatment of the newly blind. But the role of refractive errors and muscle balance in dyslexia, and the possibility that atropine intoxication and sudden enforced abstinence from alcohol may cause hallucinations and disorientation after cataract extraction, are not mentioned. The frequently-marked improvement which may occur in an eye lesion when the patient is admitted to hospital on exactly the same treatment as he had been receiving outside, is put down to the mental rest from responsibility and to a complete surrender and dependence with no concomitant feeling of guilt. Any possibility that the treatment may be applied in hospital more regularly and efficiently is ignored.

Other theories are that patients with uveitis have an excessively active sympathetic system which will function normally if a high protein and calorific diet is prescribed, and that the separation anxiety experienced by children when admitted to hospital terminates about the age of 15 months, but is then replaced by castration (*i.e.* mutilation) anxiety which is at its peak between 3 and 5 years.

Many illustrative cases are quoted. For example, in a case of sympathetic ophthalmitis, in which all other treatment had failed, the exciting eye with hypotony and a visual acuity of only hand movements was restored to 6/9 partly and J.1 by an "attack" on the patient's emotional life.

This is a book which is obviously written in all sincerity, but so much of it is based on psychological premises which some would consider suspect, that it should not fall into the hands of any but the most experienced and sceptical ophthalmologists. How far it might encourage near-quackery disturbs the mind of the reviewer. At any rate one would like to know what is the percentage of psychosomatic as compared with straightforward diseases of the eye.

As a final word of advice, "the physician must assume a dogmatic, omniscient, and self-assured manner". The authors have done just this.

CORRIGENDUM

In the article entitled "Retinal Vascular Micrometry", by M. B. Snodgrass in the September issue (*Brit. J. Ophthal.*, 1958, 42, 535), on p. 536, fourth line from the bottom, delete the word 'fifteen'.